

Treating Urothelial Bladder Cancer

Francesco Soria
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Editors

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Preface

Bladder cancer represents the most common genitourinary cancer in male population after prostate cancer and the most common in women, with around 80,000 estimated new cases during 2016 only in the United States. It is mainly a disease of the elderly, with the majority of new diagnoses occurring in the decade between 75 and 84 years. Therefore, with the aging of population, bladder cancer will become even more frequent and develop in an even bigger public health challenge in the near future. This will lead to a mandatory multidisciplinary management, which will call in not only the urologist, medical oncologist, and radiotherapist but also the general practitioner, geriatrician, and public health manager.

Moreover, after many years, novel technologies and new therapeutic agents are becoming a reality in the treatment of urothelial bladder cancer, carrying the opportunity to change the natural history of the disease. This will lead, as already happens for other cancers, to more and more individualized treatments. Therefore, one of the major challenge will be the correct selection of the right treatment for the right patient. All the figures which are taking part in the management of bladder cancer will be involved in this challenging process, and, to achieve these ambitious results, they must be open to change and improve their approach to the disease.

The idea of writing a book focused on the treatments' novelties in bladder cancer management arose after the success of the first two editions of Global Congress on Bladder Cancer. The great interest originated from the debate between all the figures involved in bladder cancer management convinced us that this would be the right time to publish a book that will be able to act as a guide in these years of change.

The dissemination of effective new diagnostic technologies and the improvement in minimally invasive radical surgery with robotic surgery along with the advent of systemic immunotherapy make the present time unique in the history of bladder cancer and open the premise for a breakthrough in disease outcome.

Are we ready for the “new era of bladder cancer”?

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Part I

Bladder Cancer Diagnosis

1. Imaging in Bladder Cancer: Can We Do Better?

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Keywords MRI – CT – FDG PET – Diagnosis – Imaging

Introduction

Bladder cancer is the most common malignancy of the urinary tract, being the seventh most common cancer in men and the 17th in women. Tobacco smoking is the most common recognized risk factor, although in a minority of cases occupational exposure to aromatic amine, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons, ionizing radiation and schistosomiasis are considered the most important predisposing factors.

The great majority of neoplasms are epithelial and among them more than 90% are urothelial tumours, except in developing countries where squamous cell carcinoma is the most common histologic type due to the high prevalence of schistosomiasis. Malignant, nonepithelial malignancies are very rare. Morphologically, urothelial tumours can be papillary or non-papillary. The former are more common (80–85% of cases) and tend to be non-muscle-invasive, low grade, multifocal tumours that arise from hyperplastic epithelium. They have an overall good prognosis, though the recurrence rates can be as high as 50%. Non-papillary tumours are the

minority (20–25%) and are more often muscle invasive and high grade, deriving from dysplasia or carcinoma in situ.

Controversial Aspects

At present, imaging studies for bladder cancer are required after muscle-invasive bladder cancer (MIBC) is diagnosed. The most important information they are required to provide are: extent of local tumour invasion, tumour spread to lymph nodes, tumour spread to upper urinary tract and other distant organs such as liver, lungs and bones [1]. In clinical practice, the evaluation of the extent of local tumour invasion means differentiating a T4 tumour, that is a neoplasm that invades prostate stroma, seminal vesicles, uterus or vagina from T3 or lower tumours. Imaging cannot accurately differentiate a T2b tumour invading the deep bladder muscle (outer half) from a T3 tumour that invades perivesical tissue. Improvement in magnetic resonance imaging (MRI) technique could theoretically help in such distinction, even though at this time the clinical significance of this kind of information may be limited.

More importantly, imaging studies are currently not considered in the initial diagnosis of bladder cancer. The most important information for treatment planning, that is differentiation of non-muscle-invasive bladder cancer (NMIBC) from MIBC, is yielded by cystoscopy. According to recent literature, MRI could be able to distinguish invasive malignancies from superficial ones with a possible improvement in patient management. If MRI is demonstrated to be reliable in classifying a neoplasm as invasive, the first diagnostic cystoscopy could be omitted. Therefore, the urologist could directly perform a TURB for definitive diagnosis and this could greatly expedite radical treatment, whilst avoiding at the same time unnecessary invasive procedures.

Bladder Cancer Diagnosis and Staging

Bladder cancer is most commonly suspected because of haematuria (80–90%) or other urinary symptoms such as urinary frequency, urgency, pelvic pain or weight loss, although it is increasingly diagnosed as an incidental finding during other imaging studies. To confirm the clinical suspicion, urinary cytology and diagnostic flexible cystoscopy are performed. The

most crucial step at this stage is to differentiate between NMIBC and MIBC. If NMIBC is diagnosed, a transurethral resection of the bladder (TURB) is performed, to completely remove all visible lesions and to make the correct diagnosis. Upper urinary tract imaging to exclude synchronous tumours is also recommended. Subsequent patient management depends on patient's and tumour's characteristics, and often entails administration of intravesical chemotherapy.

If MIBC is diagnosed at cystoscopy, patient management greatly differs because imaging studies are required for disease staging as treatment and prognosis of MIBC are determined by tumour stage and grade. If a bladder tumour has been incidentally but unequivocally visualized in previous imaging studies, such as computed tomography (CT), ultrasound (US) or MRI, diagnostic cystoscopy can be omitted and the patient can directly undergo TURB to obtain a complete histological diagnosis. TURB is mandatory to enable histopathological diagnosis and staging, which requires resection of the bladder muscle to confirm or exclude tumour invasion.

Imaging for Staging of MIBC: What Do We Do?

The purpose of imaging studies is to provide useful information to accurately choose the correct treatment plan. According to the European Association of urology (EAU) guidelines, Imaging parameters required for staging MIBC are the following:

- Extent of local tumour invasion;
- Tumour spread to lymph nodes;
- Tumour spread to upper urinary tract and other distant organs (e.g. liver, lungs, bones, peritoneum, pleura and adrenal glands).

Local staging can be achieved using equally CT or MRI, as neither of those techniques is able to accurately differentiate tumour invasion of the outer half of the bladder wall from microscopic invasion of the perivesical tissue (e.g. T2b vs. T3a). The goal of imaging studies is therefore to exclude the presence of an extravesical mass (stage T3b or higher) as shown in Fig. 1.1. There is no definitive evidence about which technique should be used preferentially. According to literature MRI has a higher accuracy compared to TC for primary tumour staging thanks to its superior soft tissue contrast, with a reported sensitivity and specificity of 93–100% and 73–

94% respectively in delineating extravesical extension (compared to a sensitivity and specificity of 85–89% and 63–95% respectively for CT) [2]. MRI examination of the bladder includes axial and coronal T2-weighted fast spin-echo imaging; axial T2-weighted fat-saturated imaging; axial T1-weighted dual-echo in-phase and opposed-phase imaging and diffusion-weighted imaging (DWI). The collecting system can be delineated in detail with static-fluid MR urography or with excretory MR urography performed with a T1-weighted fat-suppressed 3D gradient-echo sequence with gadolinium contrast excretion into the collecting system. T2-weighted images provide the optimal soft-tissue contrast. As the detrusor muscle is seen as a hypointense band against the hyperintense urine and perivesical fat, disruption of the hypointense layer is usually indicative of MIBC. On T2-weighted images, extravesical extension is seen as nodular soft tissue of intermediate signal intensity projecting into hyperintense perivesical fat. In this regard, MRI can be helpful in excluding organ invasion when CT interpretation is dubious. A potential pitfall of MRI is the evaluation of extravesical extension of the tumour, as loss of the hyperintensity of perivesical fat can be related to inflammation or post-biopsy changes and not necessarily to tumour infiltration [3]. Nevertheless, most of the studies evaluating MRI accuracy in bladder cancer local staging were performed before the widespread availability of multidetector CT. The link between gadolinium-based contrast agents and nephrogenic systemic sclerosis (NSF) is another possible concern, therefore in patient with impaired renal function at risk of developing NSF, CT should be considered as a valid alternative.

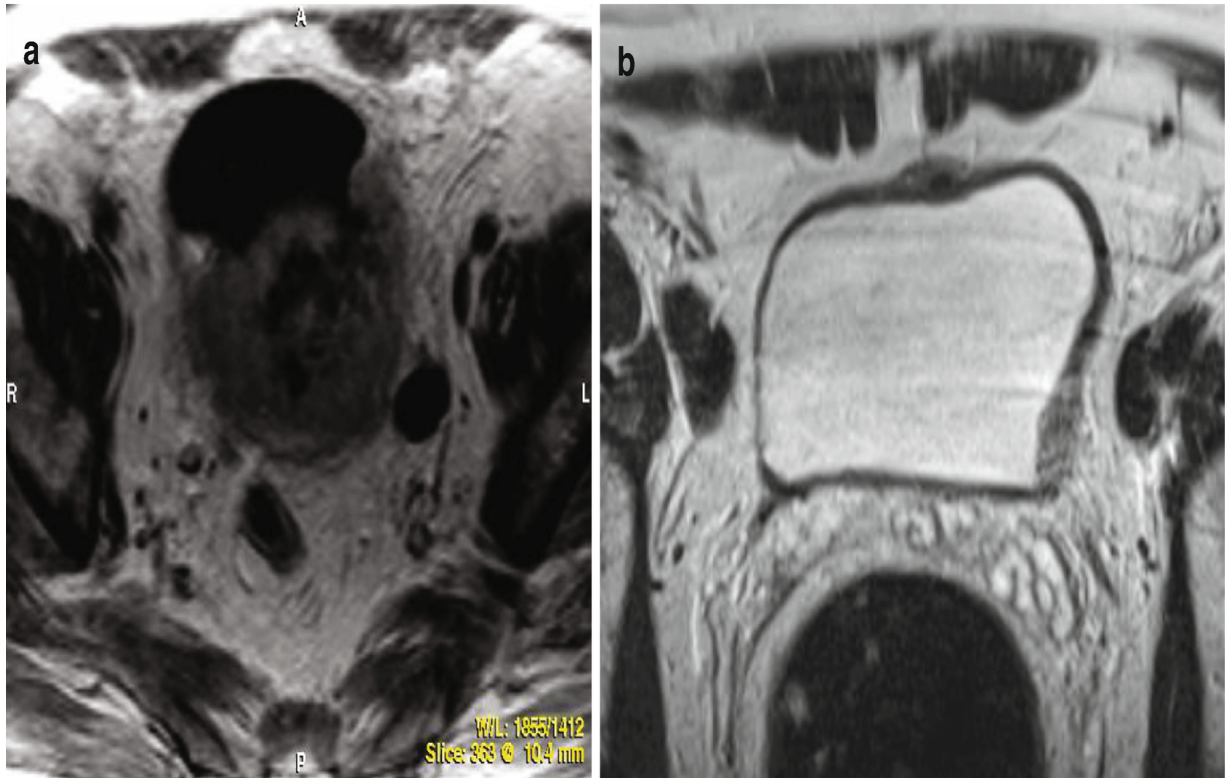


Fig. 1.1 T2-weighted images showing a T4 tumour (a) and a T3 tumour (b)

Despite the possible advantages of MRI, CT is the most commonly used imaging modality for detection and staging of bladder cancer, due to shorter acquisition time and lower susceptibility to variations due to patients' characteristics. CT is performed as an initial investigation for haematuria or for evaluation of urinary tract after diagnosis of bladder cancer. CT urography is the technique of choice and is performed in at least two phases, before and after IV administration of contrast medium [4]. When the "split-bolus" technique is used, 50 mL of iodinated contrast material is administered IV followed by furosemide (10 mg) and, after approximately 8 min, the patient is given another 60 mL of contrast. After 1 min the scan is obtained, with a simultaneous depiction of the nephrographic phase and the excretory phase (CT urography) and a reduced administration of radiation. At some institution, the nephrographic and the excretory phase are acquired separately, with a three-phase examination, because there is some evidence that intraluminal contrast could obscure small enhancing lesion, preventing the detection of early tumour enhancement during a dedicated nephrographic phase. The goal of upper tract evaluation is to exclude the presence of synchronous upper tract tumour, which can be

present in up to 2% of patients, and to find metachronous tumour, that can develop in up to 4% of patients, during follow-up (Fig. 1.2) [5]. The unenhanced phase is used to detect calcifications, blood clots and stones. During the nephrographic phase (if the bladder is not filled with contrast), a tumour appears as an early enhancing mass, while in the excretory phase the lesion appears as a filling defect. Importantly, an inflammatory or infectious process can mimic malignancy, therefore characterization with cystoscopy is always mandatory. Perivesical invasion is seen as a soft-tissue nodularity along the serosal surface, usually associated with stranding in the perivesical fat. However, fat stranding alone may represent inflammation and loss of fat planes between the lesion and adjacent organ can wrongly suggest organ invasion. Other pitfalls in CT examination of the bladder include evaluation of tumours at the bladder neck near the prostate, and small flat (sessile) lesions that can be difficult to detect. As for MRI, CT cannot be used to routinely used to differentiate MIBC from NMIBC and its accuracy increases with more advanced disease.

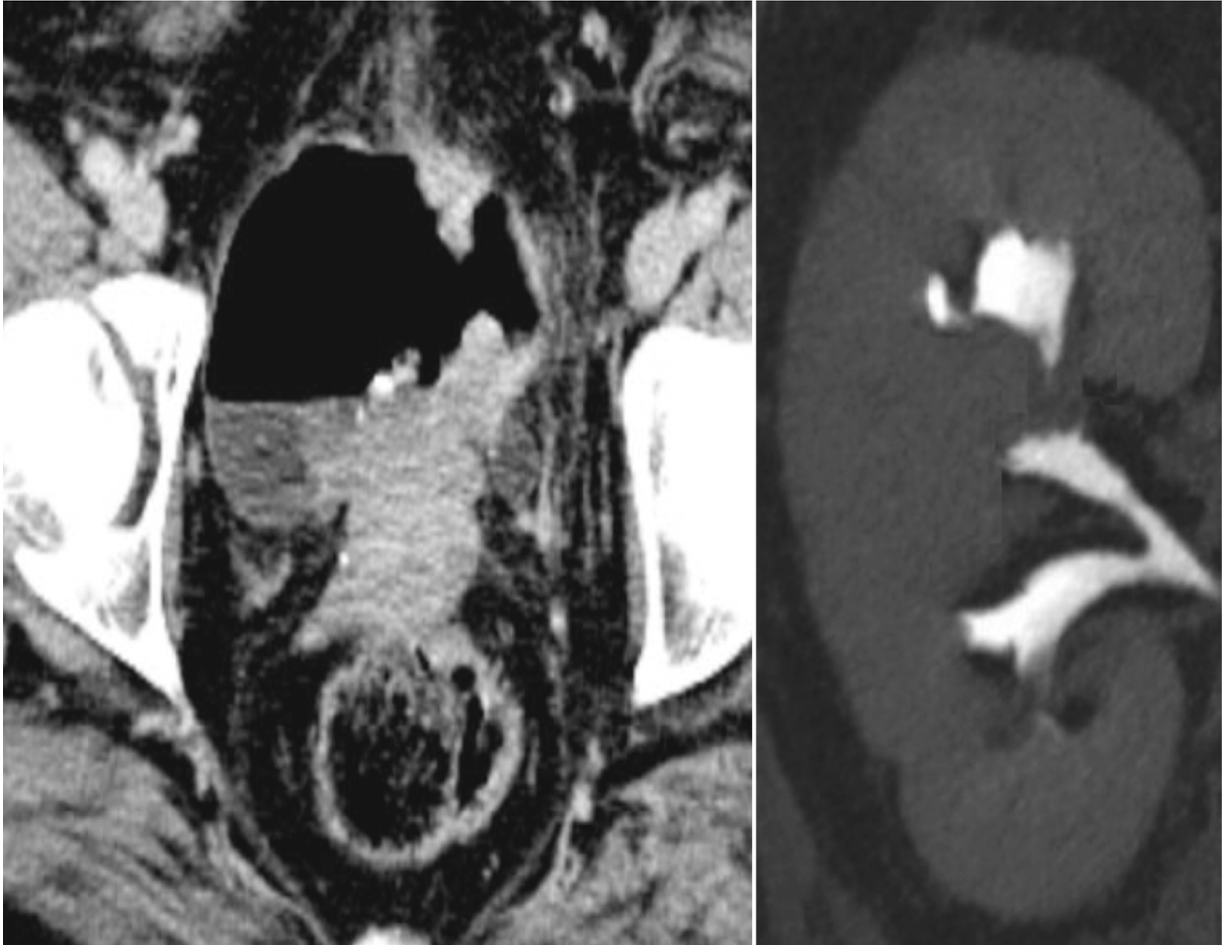


Fig. 1.2 CT examination of a patient with a locally advanced bladder cancer and a synchronous upper urinary tract tumour

As with other malignancies, the evaluation of tumour spread to lymph nodes (LN) is limited by the inherent inaccuracy of both CT and MRI. When there aren't morphological or density parameters (i.e. round shape and/or low density due to necrosis) to suggest LN involvement, assessment of LN metastases is based solely on size. As a result, sensitivity and specificity are low, because nodal enlargement may be due to benign disease and metastatic LN may be normal in size. Overall, CT and MRI have similar accuracy in detecting nodal involvement in a variety of pelvic tumours. Pathologic LN should be considered suspicious when measuring >8 mm in the pelvis and >10 mm in the abdomen in maximum short-axis diameter.

As noted above, tumour spread to the upper urinary tract is most often evaluated with CT urography, since it has the highest sensitivity and specificity (67–100% and 93–99% respectively), depending on the

technique used. If a synchronous upper urinary tract tumour is found at CT, a biopsy is required to confirm the diagnosis and provide information to aid in the choice of treatment. Evaluation of distant metastasis is also required prior to any curative intent. According to EAU guidelines, CT and MRI are the techniques of choice to detect lung and liver metastases, respectively. As bone and brain metastases are rare at the time of presentation of invasive bladder cancer, a bone scan and further brain imaging are generally not requested unless the patient has specific signs and symptoms.

Bladder Cancer Imaging: Can We Do Better?

Imaging modalities for local staging of MIBC cannot reliably distinguish a T2a from T2b tumour and a T2b from a T3a lesion. Several studies suggest that contemporary MRI technique for bladder cancer is more accurate than CT and that it could be used to exclude perivesical invasion (i.e. tumor T2b or lower). Nevertheless, as noted above, the therapeutic implications of such a distinction may still be limited. More important could be to differentiate a T2a from a T2b tumour, since the latter is more often associated with lymph nodes metastasis, which appear to have a stronger correlation with disease-free survival after cystectomy than the degree of muscle invasion itself [6]. Further improvement in MRI technique is required to reliably make such a distinction. As regards to primary tumour detection, CT cystography with negative contrast agents, such as air and carbon dioxide, and an appropriate reconstruction software have been recently used to perform virtual cystoscopy (Fig. 1.3). The reported sensitivity of virtual cystoscopy is comparable to that of conventional cystoscopy. A recent study showed that 55 of 57 bladder tumour were seen with virtual cystoscopy, and according to other authors this technique may be used to improve local tumour assessment, reaching an accuracy of 95% in categorizing T1 and T3b disease [7, 8].

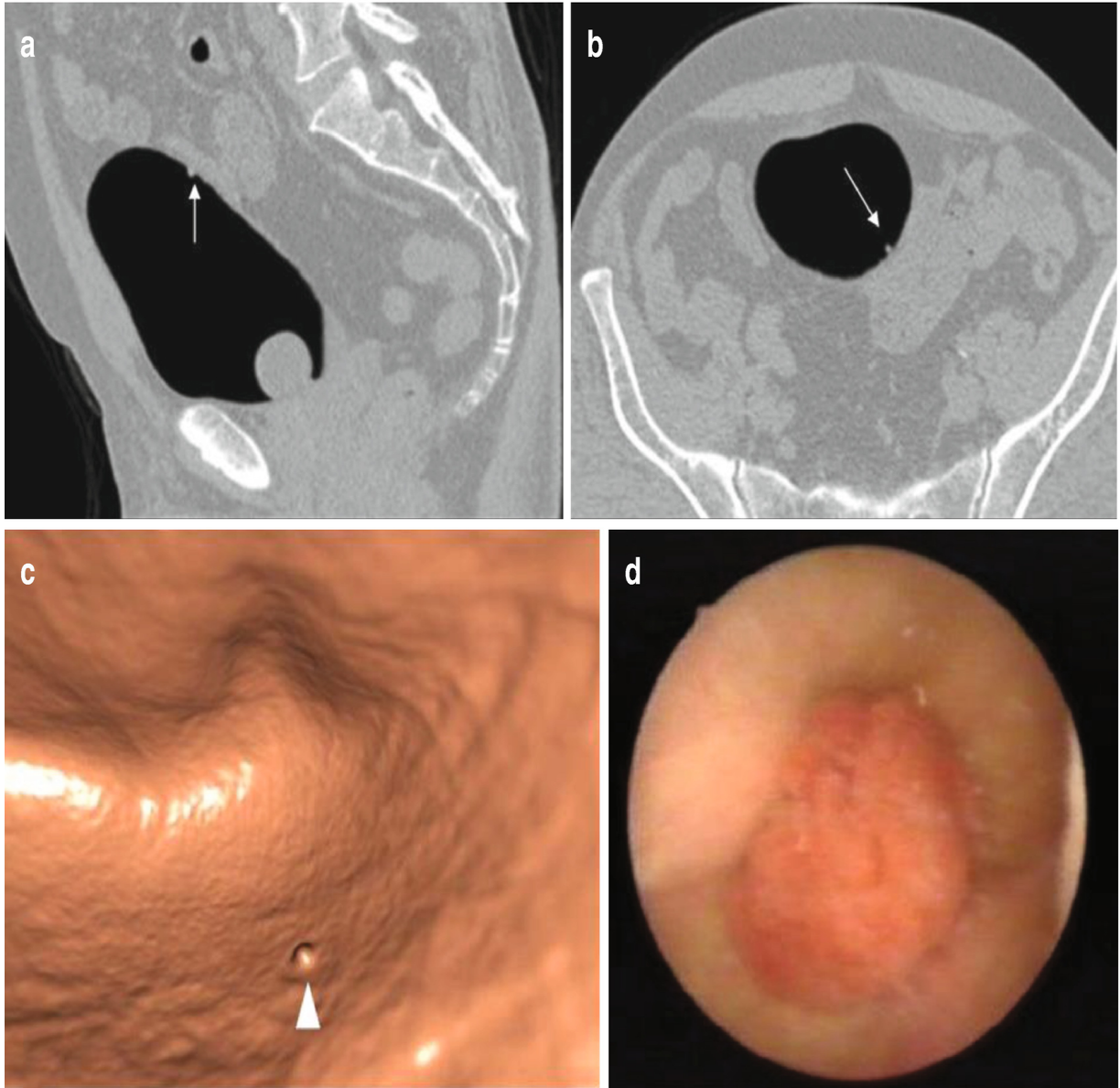


Fig. 1.3 Virtual cystoscopy of a patient with a 3 mm lesion on posterior wall of bladder dome. Sagittal (a) and axial (b) CT images; virtual cystoscopy after software post-processing (c) and cystoscopy (d) are showed

Lymph node assessment is currently limited by the “dimensional approach” which is inherently inaccurate. Currently, there is no evidence supporting the routine use of positron emission tomography (PET), but technique has been evaluated by several trials. A recent meta-analysis of FDG PET/CT for the staging and restaging of bladder cancer found that the pooled sensitivity, specificity and accuracy were 82%, 89% and 92% respectively. Particularly, there is a subset of patients that could benefit

from PET/CT, namely those with suspicious metastases in LN outside the pelvic lymphadenectomy window. At present, the trend of data available indicates an advantage of FDG PET/CT over CT and MRI in LN assessment, but larger trials are required [9].

MRI is also being investigated to improve LN evaluation. A prospective pilot study using PET/MRI showed that this technique has a greater accuracy than MRI alone in detecting metastatic pelvic LN and non-nodal pelvic malignancy. Another technique under investigation is Ultra-small Superparamagnetic Particles of Iron Oxide (USPIO)-enhanced MRI combined with DWI, which seems to improve metastases detection in normal sized pelvic LN in a short reading time. One prospective study showed a sensitivity of 65–75% and a specificity of 93–96% on a patient basis, therefore USPIO-enhanced MRI could be used to suggest which LNs outside standard pelvic lymphadenectomy should be removed.

Finally, but perhaps more importantly, MRI is currently deemed to be able to differentiate T1 from T2 tumors. As this step is the most important and often the most time- and resources-consuming, if MRI is demonstrated to be reliable in such differentiation, the first steps of the diagnostic process of bladder cancer may be changed. As noted above, T2-weighted MRI is not sufficiently accurate in differentiating MIBC from NMIBC, even though it gives a good depiction of the detrusor muscle. DWI greatly improves imaging since it allows discrimination of a thickened submucosa from inflammatory changes or fibrosis occurring beneath the tumour, that mimics muscle invasion on T2-weighted or contrast-enhanced images. Importantly, ADC values have also been demonstrated to be a biomarker predicting tumour grade, aggressiveness and response to chemoradiation therapy. The combination of T2-weighted imaging, DWI and contrast-enhanced imaging is considered to be the contemporary standard of bladder cancer imaging and local staging, and it has been showed to reach an accuracy of 92% in differentiating MIBC from NMIBC (Figs. 1.4 and 1.5). A further improvement in MRI protocol may be represented by the inclusion of Diffusion Tensor Imaging (DTI), which could help in differentiating invasive lesions when DWI and contrast-enhanced imaging are dubious. DTI may be used for qualitative assessment of detrusor muscle using fiber tractography (FT) images, where NMIBC shows even colors and regular arrangement of muscle fibers; MIBC shows irregular arrangement and direction of muscle (Fig. 1.6). DTI may be also assessed quantitatively

similarly to ADC, using fractional anisotropy (FA); the latter has been shown to be more accurate than ADC in predicting muscle invasion. The consequences of such improvements in bladder imaging are not trivial. If MRI is confirmed by larger trials to be reliable in differentiating MIBC from NMIBC, it could be included in the diagnostic evaluation of patients suspected of having bladder cancer, changing the paradigm of bladder cancer diagnosis. At present, most patients undergo the first cystoscopy, which is followed by TURB in most cases given the inaccuracy of the biopsy sample in determining muscle invasion. If for patients with NMIBC it is enough, for patients who are eventually found to have MIBC, the procedure has the only effect of delaying radical treatment. In such cases, if MRI could reliably show tumour invasiveness, surgical treatment may be offered after the first cystoscopy (Fig. 1.7), with the possible advantages of expediting radical treatment, at the same time avoiding unnecessary invasive procedures [10, 11].

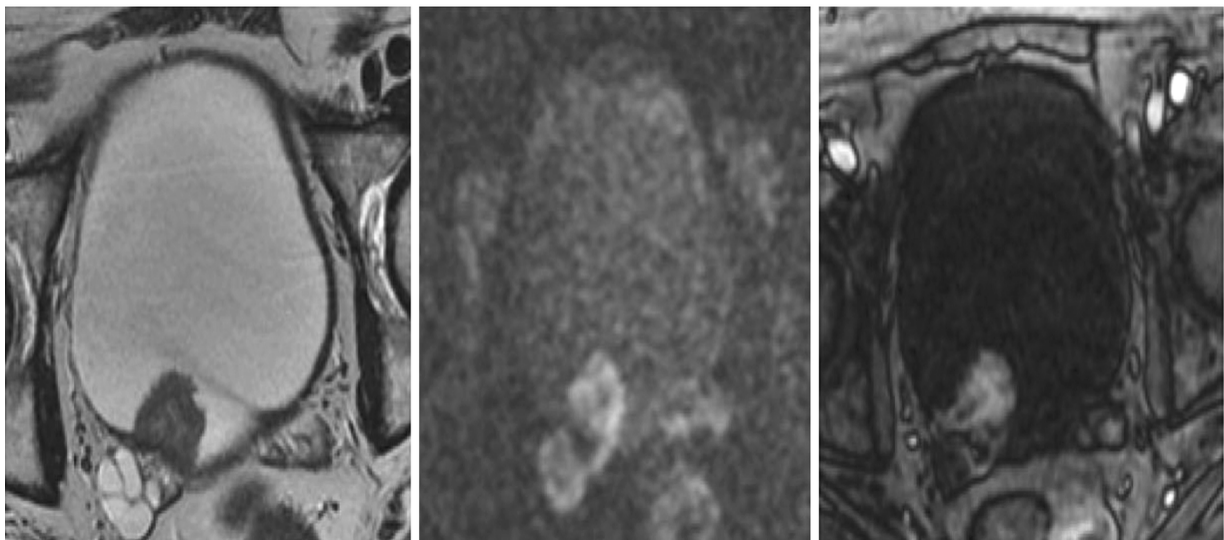


Fig. 1.4 Example of muscle invasive bladder cancer, as depicted on T2-weighted, DWI and contrast-enhanced images

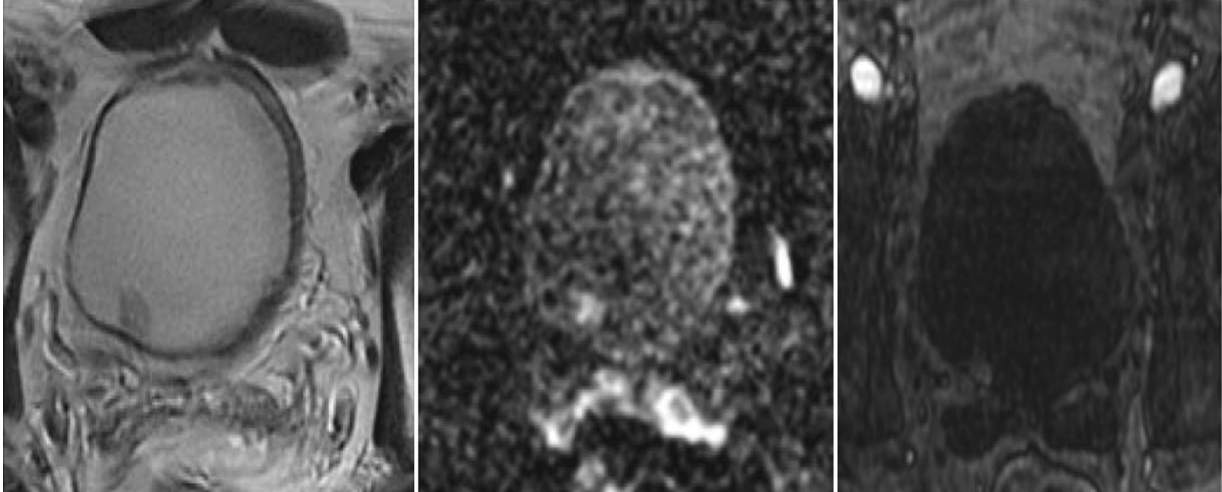


Fig. 1.5 MRI study of a patient with non-muscle invasive bladder cancer, as depicted on T2-weighted, DWI a and contrast-enhanced images

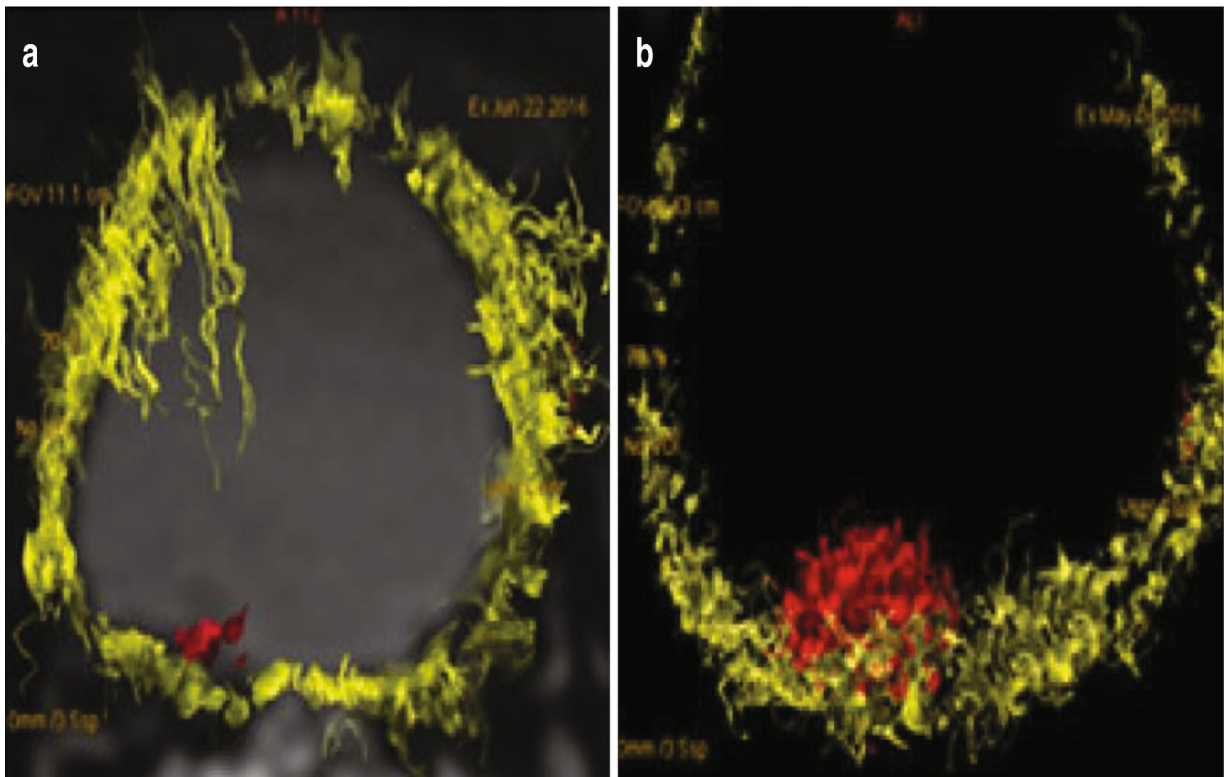


Fig. 1.6 Diffusion tensor imaging of a non-muscle invasive (a) and muscle invasive bladder cancer (b) as depicted with fiber tractography

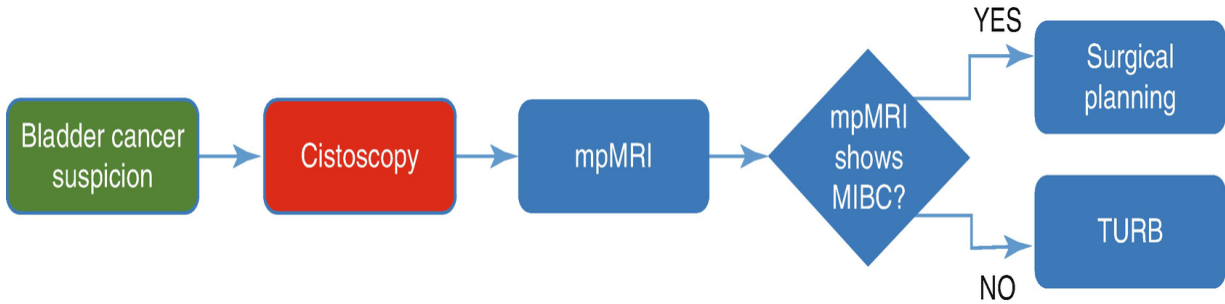


Fig. 1.7 Example of a flow-chart that includes multiparametric MRI (mpMRI) in the diagnosis and treatment planning of bladder cancer. If muscle-invasive bladder cancer (MIBC) is suspected at imaging, patient can undergo surgical consultation, without undergoing a second invasive procedure such as transurethral resection of the bladder (TURB), which is indicated only in patients with non-muscle-invasive bladder cancer

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2. New Optical Improvements in Bladder Cancer Diagnosis: Seeing Better for a Better Management?

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Keywords PDD – NBI – SPIES – OCT – CLE – New technologies

Introduction

The economical burden of bladder cancer is the most important among solid tumor malignancies [1]. This burden is mainly driven by the natural history of the disease and the subsequent risk of disease recurrence and progression of non-muscle invasive bladder cancer (NMIBC); thus, needing rigorous and recurrent treatment (transurethral resection, intravesical therapy) and follow-up (cystoscopic examination, urinary cytology and imaging) [2].

The detection of urothelial carcinoma traditionally has relied on the combination of urinary cytology and cystoscopy. White-light (WL) cystoscopy is used to visually inspect the bladder for abnormal urothelial lesions. Once a lesion is identified, transurethral resection is performed to

assess anatomopathological diagnostic and prognostic features (stage, grade, Cis, lymphovascular invasion). Whereas biology drives the natural, a complete resection of all visible lesions may also contribute to cancer control [2]. Improved visualization of urothelial lesions may facilitate detection and therefore complete resection, thereby reducing the probability of disease recurrence.

In this chapter, we discuss the current available and under evaluation tools for bladder cancer diagnosis.

Evidence Synthesis

The new imaging techniques can be classified according to their scope as macroscopic, microscopic and molecular. Macroscopic techniques include photodynamic diagnosis (PDD) and narrow-band imaging (NBI). Microscopic techniques, such as optical coherence tomography (OCT) and confocal laser endomicroscopy (CLE), provide high-resolution cross-sectional views of the tissues, likewise anatomopathological examination. By combining optical imaging with fluorescence, molecular imaging methods offer highly specific real-time visualization of cancer cells and their differentiation from healthy tissue.

Photodynamic Diagnosis/Fluorescence Cystoscopy

Concept

PDD enhances the visual contrast between benign and malignant tissue by selective accumulation of red-fluorescent porphyrins, mainly protoporphyrin IX (PpIX), in cancerous cells [3]. Two drugs have been used to diagnose bladder: 5-aminolevulinic acid (5-ALA) and its derivate, hexylaminolevulinate (HAL; Hexvix, Photocure, Oslo Norway). As these drugs are prodrugs, they lack of photoactivity themselves. After transportation into the urothelial cell, they are incorporated in the conventional cellular haemobiosynthesis metabolism. In bladder cancer cells and precancerous tissue, altered enzyme activities lead to a significant accumulation of PpIX [4]. When the bladder wall is illuminated by blue light (<380–440 nm), the PpIX in malignant tissue emits red fluorescence (<635 nm) in contrast to the normal/benign urothelial tissue (which appears blue) [5]. The different appearances of malignant and normal tissues can be

visualized in real time during either diagnostic/office cystoscopy or TURBT (Fig. 2.1).

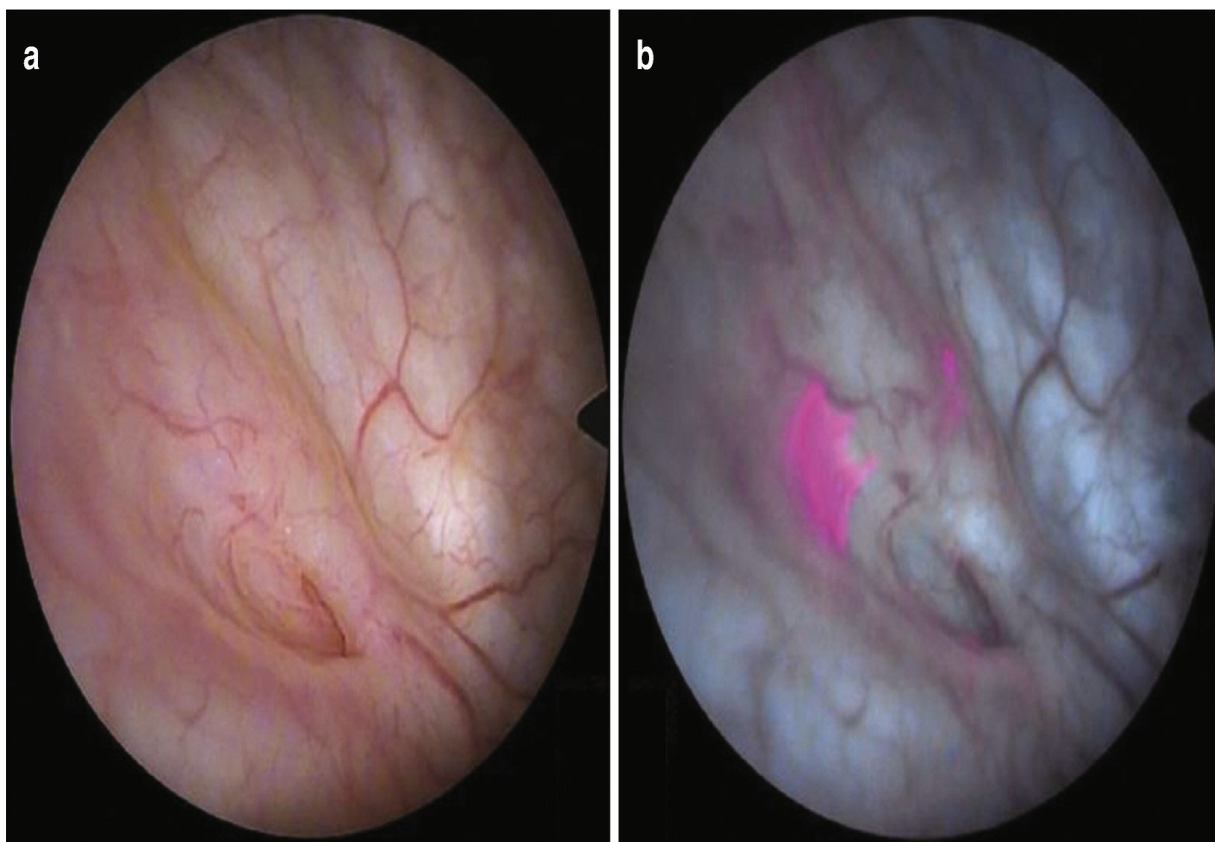


Fig. 2.1 Example of carcinoma in situ under white light (a) and under photodynamic diagnosis (b)

Detection

PDD has been in use for two decades using 5-ALA and, more recently, HAL. European Association of Urology guidelines include PDD as an option if available when a high-grade cancer is suspected (either positive urinary cytology or previous history of high-grade bladder cancer [2]. Multiple studies have validated the increased ability of PDD to detect both papillary and plane (CIS) lesions. Burger et al. reported in a recent meta-analysis that at least one additional papillary tumor (pTa-pT1) was identified in 25% of patients when using PDD [6]. A pooled analysis of three randomized controlled trials has shown an increased detection rate of CIS from 75 to 87% with PDD versus WL [7–9]. Several studies have also suggested that using PDD would allow a more complete tumor resection [10, 11].

Impact on Oncological Outcomes

Several recently reported phase 3 trials have evaluated the potential for ALA and HAL to reduce the risk of recurrence and increase the recurrence-free interval (Table 2.1) [10–19].

Table 2.1 Recurrence-free and progression free-survival estimates in the studies evaluating photodynamic diagnosis in non-muscle-invasive bladder cancer

Study	Year	Prodrug	Interval since resection	RFS, %		PFS, %	
				PDD	WLC	PDD	WLC
Grossman (<i>n</i> = 516)	2012	HAL	Median follow-up:	38	32	–	–
			12 mo	78.4	67.5	97.6	95.6
			24 mo	68.2	54.4	96.0	93.0
Hermann et al. (<i>n</i> = 145)	2011	HAL	4 mo	83.1	68.9	–	–
			12 mo	69.5	52.7		
Stenzl et al. (<i>n</i> = 359)	2011	5-ALA	12 mo	68.9	74.4	89.4	89.9
Stenzl et al. (<i>n</i> = 551)	2010	HAL	9 mo	53	44		
Schumacher et al. (<i>n</i> = 300)	2010	5-ALA	12 mo	55.1	55.9	91.1	89.1
Burger et al. (<i>n</i> = 419)	2009	5ALA	12 mo	94	78		
			24 mo	87	71		
			36 mo	80	67		
		HAL	12 mo	92			
			24 mo	84			
			36 mo	82			
Denzinger et al. (<i>n</i> = 46)	2008	5-ALA	48 mo	91	69		
			96 mo	80	52		
Denzinger et al. (<i>n</i> = 301)	2007	5-ALA	24 mo	88	73		
			48 mo	84	64		
			72 mo	79	54		
			96 mo	71	45		
Burger et al. (<i>n</i> = 101)	2007	5-ALA	85 mo	71	45	98	98
			12 mo	57	39		
			36 mo	41	27		
			60 mo	41	25		

Study	Year	Prodrug	Interval since resection	RFS, %		PFS, %	
				PDD	WLC	PDD	WLC
Babjuk et al. (<i>n</i> = 122)	2005	5-ALA	10–15 wk	92	68		
			12 mo	66	39		
			24 mo	40	28		
Filbeck et al. (<i>n</i> = 191)	2002	5-ALA	12 mo	90	74		

To our knowledge, no data to date have suggested that PDD is associated with a reduction in disease progression.

Impact on the Economical Burden

Several studies have documented that bladder cancer is the most expensive cancer from diagnosis to death. Patients who are diagnosed at NMIBC stage are the most costly among bladder cancer patients.

Cost analyses for using PDD suggest that its use can reduce the overall cost of bladder cancer care. Sievert et al. reported that the cost of a TURB would be reduced by \$187, representing a 9.2% reduction in the cost of care by eliminating the need for site-directed biopsies of normal-appearing mucosa and a 20% reduction in the need for a secondary resection within 6 months after the initial one [20]. Burger et al. estimated that an annual savings of \$224 per year resulted from using PDD according to data from a randomized control trial [14].

Limitations

The main drawback of PDD use is the false-positive diagnosed lesions. The rate of false positive lesions has been reported to be up to 40% on a per-lesion basis and range from 10 to 12% on a per-patient basis in recent clinical trials [17]. Of course, these numbers can be lowered with PDD experience as a so-called “learning curve” exists in using PDD. Other causes of false-positive florescence include tangential imaging and inflammation (prior TURB and intravesical therapy).

Narrow-Band Imaging

NBI (Olympus Corp. Tokyo) is a relatively recent macroscopic technique of endoscopic imaging that improves tumor detection without the need for drug intravesical instillation. By using special filters, the light spectrum is

reduced to its blue (415 nm) and green (540 nm) components, which are well absorbed by haemoglobin. As a result, enhanced contrast between the mucosa and blood vessels is achieved and pathologically well-vascularized lesions are clearly enhanced (Fig. 2.2). Likewise PDD, NBI improves detection [21]. In 2007, Bryan et al. were the first to publish NBI cystoscopy findings in 29 patients with recurrent bladder tumors [22]. The authors found 15 additional tumors in 12 patients, in comparison to those detected with WLC. A prospective randomized single-center study of 220 cases demonstrated better detection rates than those achieved with WLC (95% vs. 68%, respectively) [23]. The effect of NBI on therapeutic outcomes has not yet been confirmed; however, it seems obvious that better visualization/detection would offer better local control, and increase the recurrence-free intervals.

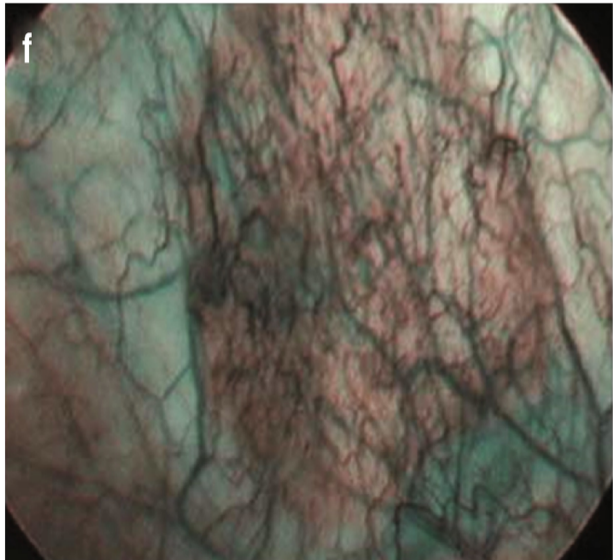
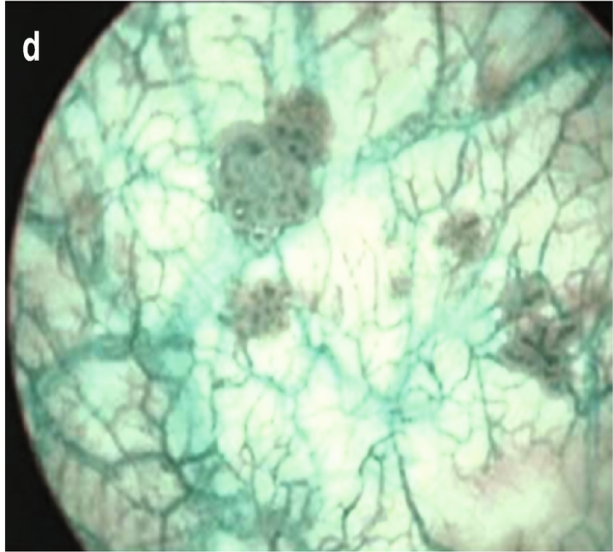
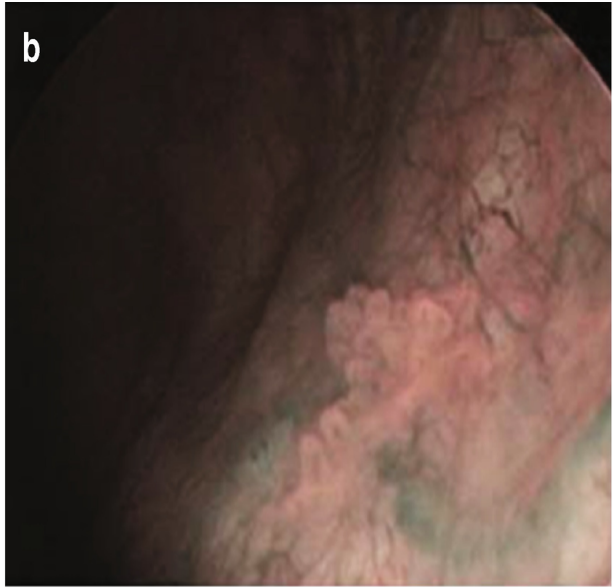
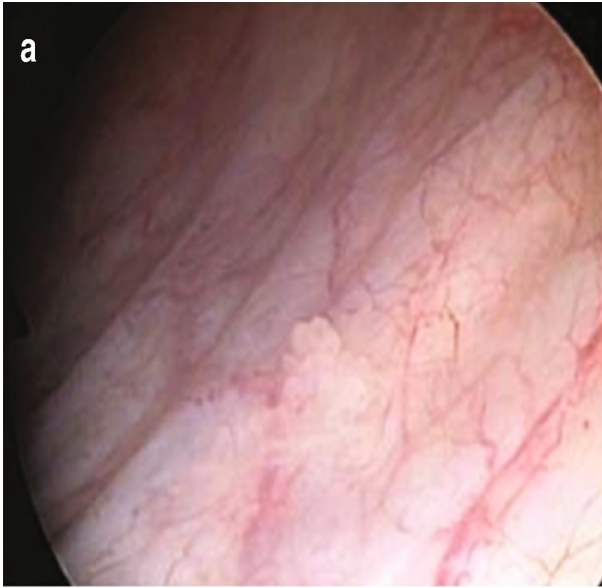


Fig. 2.2 Examples of bladder cancer lesions under white light (**a, c, e**) and under narrow band imaging (**b, d, f**)

Storz Professional Image Enhancement System

Based on similar technology, Storz has recently introduced the Storz Professional Image Enhancement System (SPIES). The addition of different colors (e.g. orange or violet) to the image obtained by reflected blue- and green-spectrum light offers three different viewing options depending on needs in various clinical situations. SPIES is currently at the early clinical study stage of investigation.

Microscopic Imaging

Microscopic imaging techniques, including OCT and CLE, are currently in the early stages of experimental research. Both of these techniques reveal the histopathological structure of the tumor during cystoscopy.

The OCT technique provides real-time high-quality cross-sectional images of superficial tissues. Similarly to ultrasonography, this technique uses the signal created by waves reflected from various tissue surfaces. In contrast, however, it uses the waves of the near-infrared light spectrum (890–1300 nm). This allows for tissue imaging at 10–20 μ m resolution and up to 2 mm in depth, which is sufficient to identify most urothelial tumors (Fig. 2.3). OCT differentiates between abnormal and healthy urothelium, and although it does not differentiate tumor grades, it allows for assessment of tissue infiltration status. Thanks to the probe, compatible with the cystoscopy equipment, tumor stage assessment can be conducted during both office cystoscopy and TURB procedures. Several available studies estimated the sensitivity and specificity of the technique at 90–100% and 65–89%, respectively [24]. Despite the initially promising findings, OCT is difficult to use in daily practice. Scanning the entire bladder to search for neoplastic lesions is a laborious task.

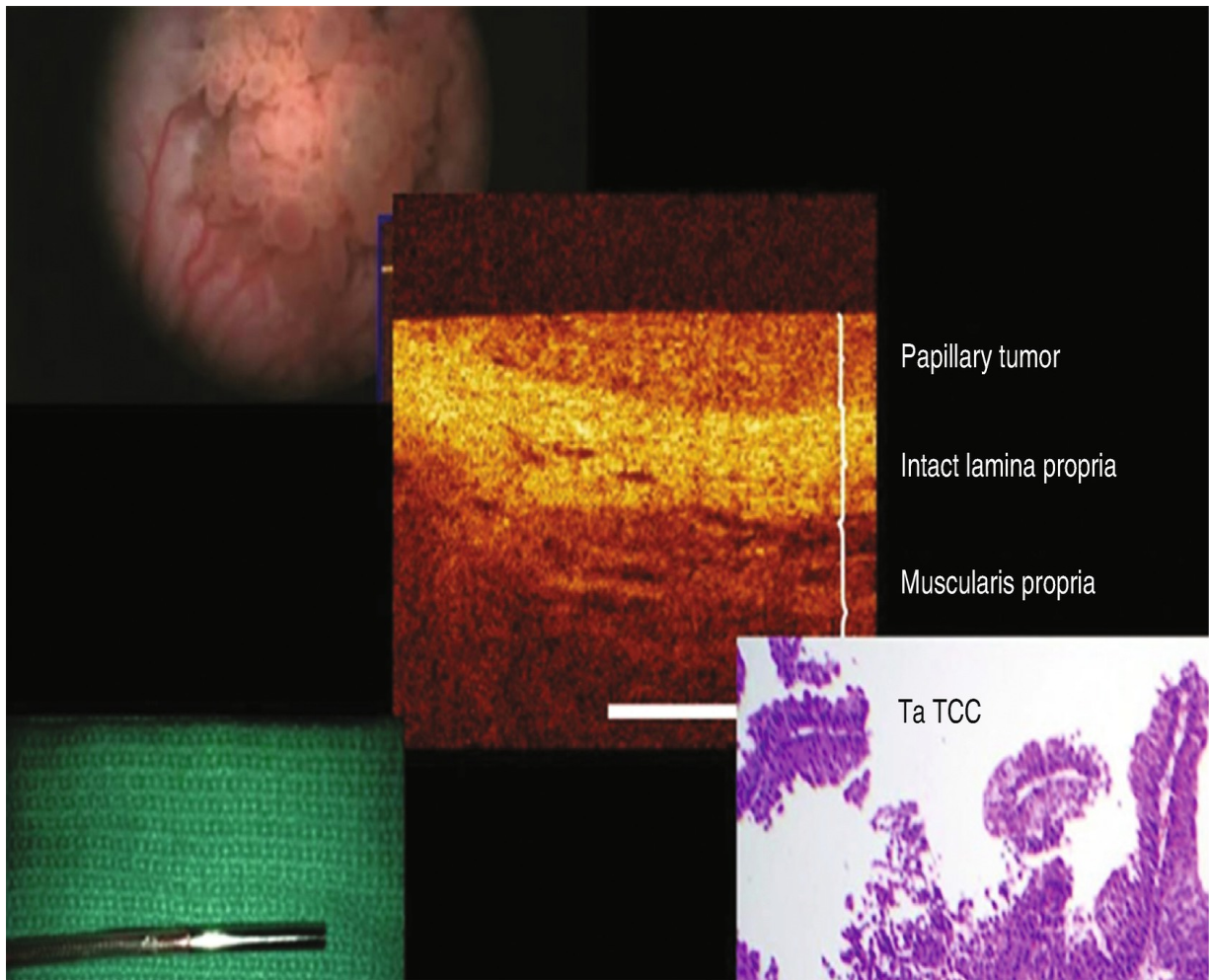


Fig. 2.3 Optical coherence tomography in bladder cancer lesion and comparison with pathologic image

CLE uses a fiber optic probe bundle inserted into the lumen of an operating cystoscope and a fluorescent agent administered intravesically to obtain real-time microscopic images of the examined tissue. CLE has already been successfully used in the diagnostic endoscopy of gastrointestinal tumors. With the reduced caliber of the probe, the technique can be used in endourology. Because of its high resolution (2–5 μm) and depth of imaging penetration (240 μm), CLE helps to achieve detailed images of tissue structure and evaluate the appearance of individual cells. This technology makes it possible to obtain data on tissue differentiation status and thus distinguish high from low-grade urothelial carcinoma.

Raman Spectroscopy

Raman spectroscopy relies on the inelastic scattering of photons following interaction with intramolecular bonds. Raman spectroscopy uses infrared light (785–845 nm) to excite intrinsic chemical bonds in order to create optical contrast. Raman spectroscopy was able to differentiate the normal urothelium from urothelial carcinoma, grade and tumor invasiveness [25].

Multiphoton Microscopy

Autofluorescence of cells and extracellular matrix components in multiphoton microscopy is obtained after the simultaneous absorption of two or more photons of lesser energy. Multiphoton microscopy makes use of intrinsic tissue fluorophores. In a recent study, *ex vivo* tissue MPM analysis allowed differentiation of normal urothelium from malignant structures [26].

Scanning Fiber Endoscopy

Scanning Fiber Endoscopy (SFE) employs a 1.2 mm wide angle, color, high resolution flexible endoscope. The image is generated by red, green and blue laser scanning of tissues and analysis of backscattered light. SFE can be used in automatic devices to create a panoramic view of the mucosa.

Ultraviolet Autofluorescence

Ultraviolet autofluorescence is designed to distinguish normal, inflammatory urothelium and urothelium carcinoma by discriminating variances in their molecular contents. After exposure to UV laser radiation, endogenous fluorophores emit autofluorescence diagnostic signals that are converted into an intensity ratio between different wavelengths. A recent *in vivo* pilot study demonstrated the feasibility of this method in differentiating urothelial carcinoma from normal urothelium [27].

Molecular Imaging

Molecular imaging is achieved by combining optical (macroscopic and microscopic) imaging and intravesical administration of fluorescent-labeled elements, such as antibodies, peptides, and other molecules, which selectively bind to cancer cells.

Conclusion

White light cystoscopy, which is the standard of care has improved with the incorporating high-definition, 3-chip cameras, and thus provides optimal endoscopic imaging of the urinary tract. The application of new imaging technologies offers the opportunity to improve detection and staging, thereby improving the precision of decision-making for personalized treatment and follow-up scheduling. Photodynamic diagnosis has to date the more evidence-based data including decrease in disease recurrence. Emerging technologies could provide real-time evaluation and thereby bring the microscope into the office cystoscopy and in the operative room.

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3. Enhancing the Quality of Transurethral Resection: The Importance of a Complete TURB and the En-Bloc Resection

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Introduction

Classical **Trans-Urethral Resection of the Bladder (TURB)**, executed with White Light (WL), is worldwide considered as the gold standard for diagnosis and treatment of Bladder Cancer (BC).

The specimens obtained by TURB are fundamental in order to establish both grading and staging of the disease, leading towards the most effective therapeutic approach.

In this context, the details that make the difference between a “Good-quality TURB” and a simple TURB have to be always considered, even if

TURB is one of the first endoscopic procedures executed by training residents.

Additionally, despite decades of ameliorations in technique and instruments, TURB is far from being limits-free.

The first problems often arise from an inadequate specimen that doesn't contain the DM, which ranges from 20% up to 60% of cases [1]. Additionally, upstaging to invasion of the muscularis propria following re-TURB is directly related with the presence of Detrusor Muscle (DM) in the first TURB [2].

Moreover, up to 40% of resections are incomplete, leading to an increased risk of recurrence. Not surprisingly, the most likely source of early recurrences are the margins of the base of the original resected tumour [2, 3].

Recurrence in BC is extremely common, with only 63% of patient being disease-free at 5 years, and this is the most important limitation in the treatment of BC with TURB. Interestingly, a multivariate analysis showed that two factors may decrease the risk of recurrences: the use of the bladder diagram and being a senior surgeon (Fig. 3.1) [1, 3]. A summary of TURB limits and bibliography are reported in Table 3.1. See also the flow-chart reported in (Fig. 3.2).

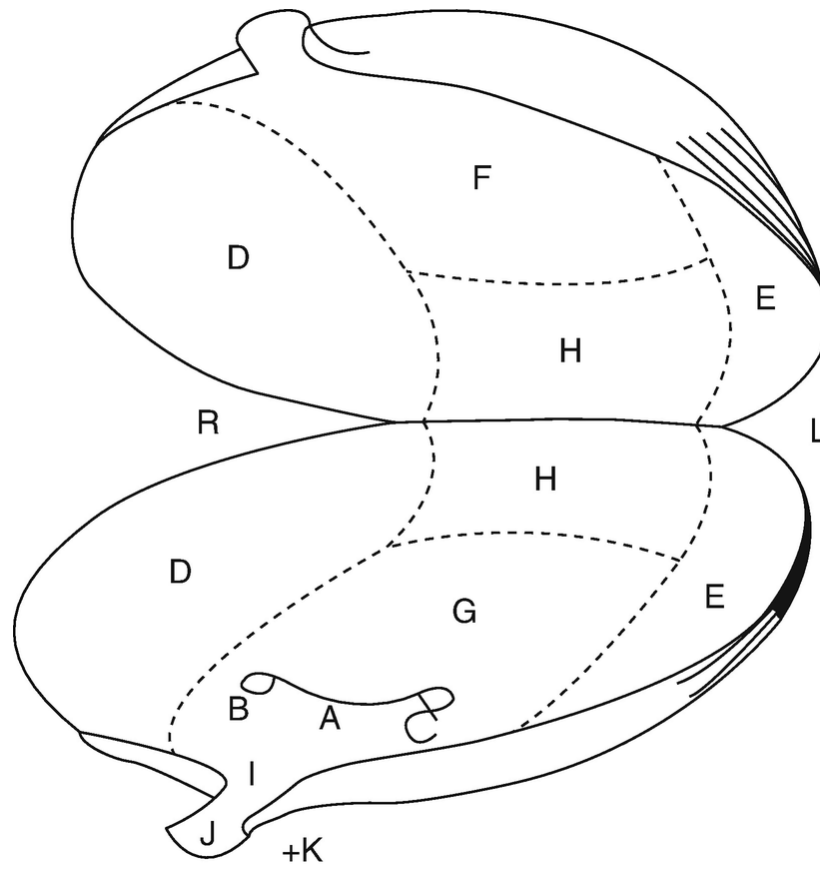


Fig. 3.1 Elements of bladder diagram

Table 3.1 Limits and relative references of White Light Trans-Urethral Resection of the Bladder (WL-TURB)

Features	Incidence	References
Residual tumour	15–40%	Grimm [3] van Rhijn [25]
Recurrence	50–80%	Grimm [3] Herr [26]
Understaging	20–60%	Brausi [1] Thomas [7]
DM absence	11–50%	Maruniak [27] Mariappan [28]

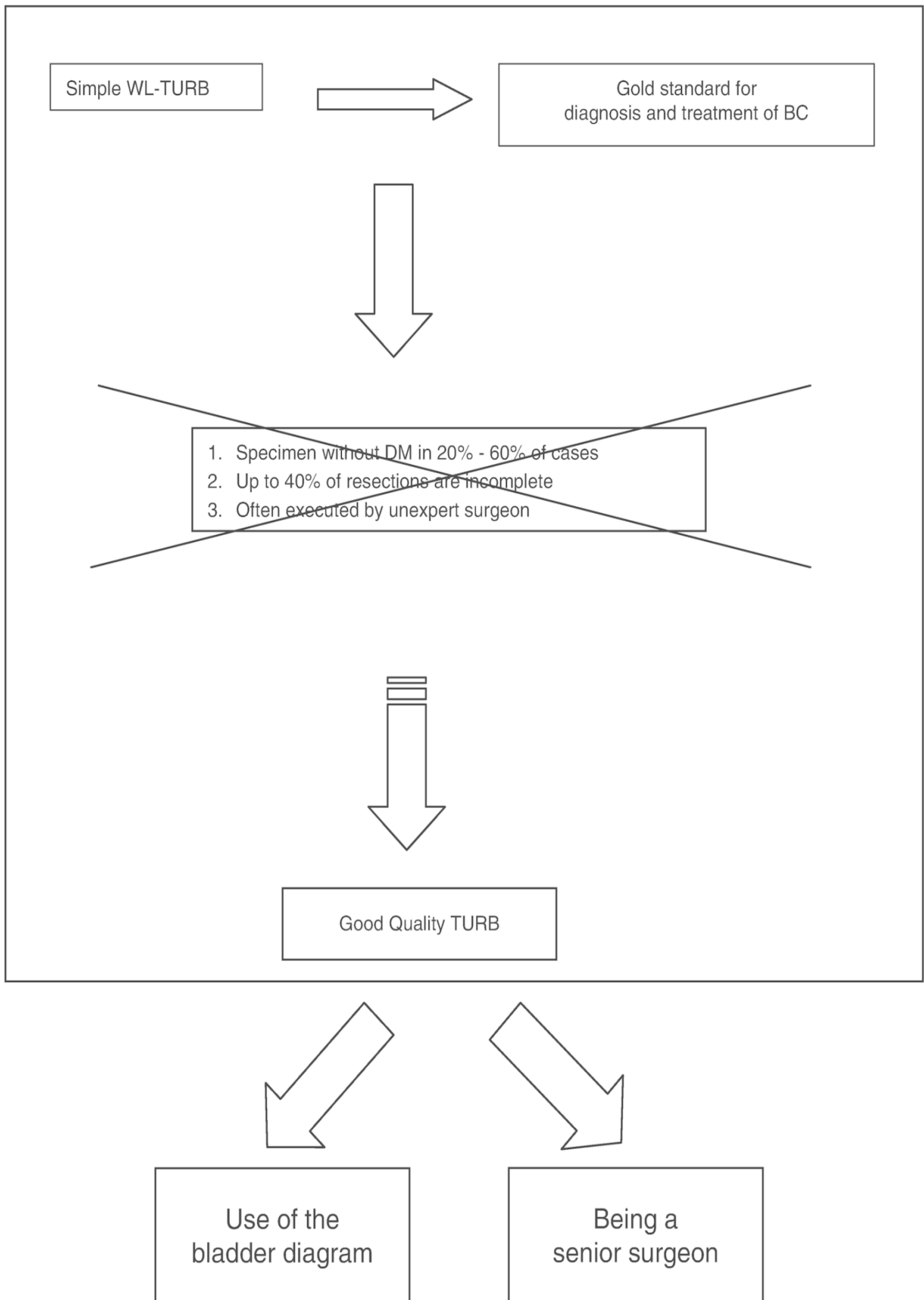


Fig. 3.2 Flow-chart: what are the most important limits of classical TURB and how can we improve it?

Highlights

The most important limits of classical TURB (absence of DM in the specimen and resections often incomplete), usually performed by unexpert surgeon, may lead to high risk of BC recurrence. Being a senior surgeon and the use of bladder diagram may help to overcome these limits, performing a “Good-quality TURB”.

How to Perform a Good Quality Turb

The Importance of Turb Check List

The choice of the treatment with the best oncologic results plays a fundamental role in terms of prognosis. As a matter of fact, a TURB considered as “adequate” may drastically modify the disease clinical course. In this context, there are several alternatives to improve the TURB technique; we will report the best technical approach, according to the most recent data literature.

The implementation of a stepwise approach may be the answer to the limitations above mentioned. Two authors published two different models of “Bladder Tumour Checklist”, as respectively reported in Tables 3.2 and 3.3 [4, 5]. In this context, Anderson and Coll. demonstrated an increase of 2.9% in specimen muscle inclusion when the items reporting increased from 5 to 8 [5].

Table 3.2 “Bladder tumour checklist” according to Pan et al. [4]

Pre-operative consultation	Intra-operative consultation	Post-operative consultation
About patient: – History – Physical examination	Equipment	Complications
Holding area: – BC history – Most recent BC – Anaesthesiology – Labs check	Intra-operative documentation	

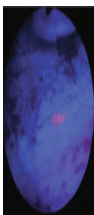
Table 3.3 “Bladder tumour checklist” according to Anderson et al. [5]

Prognostic factors	Alternative answers					Notes
Number of lesions	1	2–5	≥5	Diffuse		
Size of the largest lesion	≤1	1–3	≥3			Use the end of cutting loop as reference (approximately 1 cm wide)
Description of the main characteristics of the tumours	Sessile	Nodular	Papillary	Flat		
Presence of Carcinoma In Situ (Cis)	Yes	No	Suspicious			
Report 2010 American Joint Committee on Cancer (AJCC)	cTis	cTa	cT1	cT2	cT3	cT4
<i>Intraoperative processes</i>						
Bimanual examination under anaesthesia	Yes			No		
Visually complete resection	Yes			No		
Visualization of DM in resection base	Yes			No		
Visualization of perforation	Yes			No		

Additionally, the enhancement of intra-operative vision may be obtained through different modalities, as specified in Table 3.4: three specifically regarding the TURB technique (i.e. Computerized Video-TURB, Continuous Flow Resectoscope and Bipolar Loop) and two regarding improving in visualization PhotoDynamic Diagnosis (PDD) and Narrow Band Imaging (NBI) [6] (Table 3.4).

Table 3.4 Enhancement modalities of intra-operative vision during TURB

Technical improvement	Images	Main characteristics	Advantages	References
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Technical improvement	Images	Main characteristics	Advantages	References
Bipolar Resectoscope		– Radiofrequency energy to create a plasma field in the saline irrigant used for the procedure – Temperature ranges from 40 to 70 °C limiting the thermal energy at the site of contact and within adjacent tissues	– Clear cut with minimal visible charring – Superior hemostasis – Better quality of tissue for pathologist with less thermal artifact and cytologic changes – No or less obturator nerve stimulation	Xishuang [29] Del Rosso [30] Mashni [31] Venkatramani [32] Zhao [33] Cui [34]
Photodynamic diagnosis		– Pre-operative intravesical administration of hexyl-aminolevulinat (HAL) (within 1 h before the TURB) – Its metabolic product, protoporphyrin IX accumulates especially in high grade and CIS lesion, compared with normal tissue. When it is illuminated with blue light it emits red fluorescence, and can be used to visualize BC that should not be seen using WL	– PDD improves detection rate of BC and reduces recurrence rate – PDD-guided biopsies are recommended in the European Association of Urology (EAU) guideline in patients when cytology is positive or when high-risk exophytic tumour is expected (grade of recommendation B)	Jocham [35] Stenzl [36] Mowatt [37] Grossman [38] Burger [39] Rink [40] Lamm [41] Kamat [42] Gakis [43]
Narrow band imaging		– It is based on the fact that tumours often are well vascularized – It uses two specific wavelengths: blue (415 nm) and green (540 nm), which are both strongly absorbed by haemoglobin. This results in enhanced contrast between hypervascular tissue and normal mucosa	56. NBI-assisted TURB has higher sensitivity and specificity and lower recurrence rate comparing with WL-TURB 57. Visualization of tumours is better with NBI compared with WL	Bryan [44] Cauberg [45] Tatsugami [46] Geavlete [47] Chen [48] Kobatake [49] Herr [50] Geavlete [51] Herr [52] Naselli [53] Naito [54]

Highlights

A TURB considered as “adequate” may drastically modify the disease clinical course. There are several alternatives to improve the TURB technique:

- The use of “Bladder Tumour Checklist”;
- The enhancement of intra-operative vision obtained through different modalities: Computerized Video-TURB, Continuous Flow Resectoscope, Bipolar Loop, PDD and NBI.

Surgical Technique

Complete removal of visible neoplastic tissue should be the primary goal of any TURB.

The resection of suspicious lesions for BC and/or random biopsies over the whole bladder in case of positive urinary cytology, multiple lesions or T1 tumour, should be performed using the bladder diagram, in order to have the most precise location of the lesions (Fig. 3.1) [7].

The depth of the resection has to involve DM in order to have a correct staging; nevertheless the bladder integrity has always to be preserved.

Extreme care should be taken to prevent bladder perforation, as this seems to be a relatively common (up to 50%) complication when the operator is a training resident [8].

A meticulous and throughout haemostasis should always complete the procedure.

Highlights

- Complete removal of visible neoplastic tissue;
- Use of bladder diagram, in order to have the most precise location of the lesions;
- The depth of the resection has to involve DM;
- The bladder integrity has always to be preserved with prevention of bladder perforation and meticulous haemostasis.

The Importance of Pathologist’s Report

The outcome of TURB may be influenced not only by the quality of the intra-operative procedures, but also by the specimen analysis. There are five items considered as essential in the pathological report:

1. pT1 sub-staging World Health Organization (WHO)-1973 and WHO-

2004 classification

2. Presence/absence of Carcinoma In Situ (Cis)
3. Lymphovascular invasion
4. Histological variants.

The pT1 substaging is not included in the seventh edition of the TNM Classification, and it was not recommended by WHO or ISUP, but some form of estimate of lamina propria invasion in pT1 tumors is strongly advocated by clinicians [9].

Possible reasons for T1 substaging limited adoption may be found in the difficulty to assess lamina propria invasion due to thermal damages, inadequate orientation of specimens (due to TURB itself), and reduced inter- and intra-observer agreement [10–13].

Three different method of T1 substaging have been proposed. Orsola et al. firstly purposed an anatomical method using the infiltration of muscularis mucosa as cut-off [14]. More recently two other methods have been introduced, both measuring the quantitative micrometric invasion. The one published by van Rhijn et al. divides the depthless of the invasion into T1 m (<0.5 mm) and T1e (>0.5 mm), while the one postulated by Patriarca et al. into T1ROL1 (<1 mm) and T1ROL2(>1 mm) (ROL: Rete Oncologica Lombarda) [15, 16].

When comparing different sub-staging modalities, ROL and T1 m/T1e reached the same feasibility rate (99.6%), whereas the feasibility of the T1a/T1b/T1c method was documented to be 76.0% (Table 3.5) [17].

Table 3.5 Difference among the three methods of T1 substaging

System	5-year recurrence-free rates (%)	5-year progression-free rates (%)	Feasibility (%)
ROL1	53	92	89.5
ROL2	61	81	89.5
T1 m	50	91	86
T1e	61	84	86
T1a	55	89	57

System	5-year recurrence-free rates (%)	5-year progression-free rates (%)	Feasibility (%)
T1b/T1c	53	78	57

Perspective studies are advocated to corroborate the results of this investigation and support the clinical role of substage for pT1 High Grade (HG) BC patients.

Highlights

- pT1 sub-staging, grading with both WHO-1973 and WHO-2004 classification, presence/absence of CIS, lymphovascular invasion, histological variants are considered as essential items in the pathological report.
- The pT1 substaging, strongly advocated by clinicians, as to be reported by pathologists, using one of three available classifications (Orsola, van Rhijn, ROL).

Improving Surgical Quality of Turb

Teaching Program for Residents

Too often TURB is not given the importance it deserves, often left as the last operations of the day and done by improperly trained surgeons.

This comes as a surprise considering that we are dealing with a malignant lesion that, if not properly treated can, have a huge impact on patients' life.

Regarding this issue Hurle et al. implemented in 2005 a teaching program at Humanitas that showed to be an independent outcome predictor factor to improve quality of TURB both in residents and consultant surgeons [18]. The method consisted in the presence of a consultant physician during all TURB performed by residents, the institution of a video-TURB archive for revisions, and weekly multidisciplinary discussion meetings between urologists and genito-urinary pathologist.

In the study the increase in rate of DM in the specimen was from 59 to 82% after the teaching program, this reinforce the need for TURB to be stringently taught and efficiently performed.

En-Bloc Turb

Despite the excellent level of expertise that TURB has reached in the past years, there are still some drawbacks that should be addressed. Such issues are risk of tumor seeding, incomplete resection, thermal damage of specimen's margin, and a non-negligible rate of absence of DM.

In the last years WHO:

En-bloc Resection of Bladder Tumors (ERBT) has gained more and more popularity among urologists as it may represent a solution to the cited issues. In table below we report a summary of all the studies regarding feasibility and safety of EBRT (Table 3.6).

Table 3.6 Summary of all the studies regarding feasibility and safety of EBRT

Item	N°	%
Number of studies	22	
Total patients	1124	
Total lesions	1420	
Complications	43	43/1124 (3.8%)
Grade III complications (according to Clavien-Dindo)	12	12/1124 (1.1%)
Conversion to classical TURB	61	61/1124 (5.4%)

ERBT has been shown to obtain higher DM rates in comparison with TURB (up to 100%); the presence of DM in the specimen is of extreme importance as it associate with progression-free survival and may prevent the need for re-TURB [19]. Furthermore, Ukai et al. showed that when en-bloc technique was used the resection was complete in 98% of cases [20]. Figures 3.3 and 3.4 show two specimens obtained by ERBT: Fig. 3.3 shows a specimen of low-grade, non-invasive urothelial cell carcinoma that has been resected by ERBT technique; Fig. 3.4 shoes a specimen of high grade, T1 urothelial cell carcinoma.

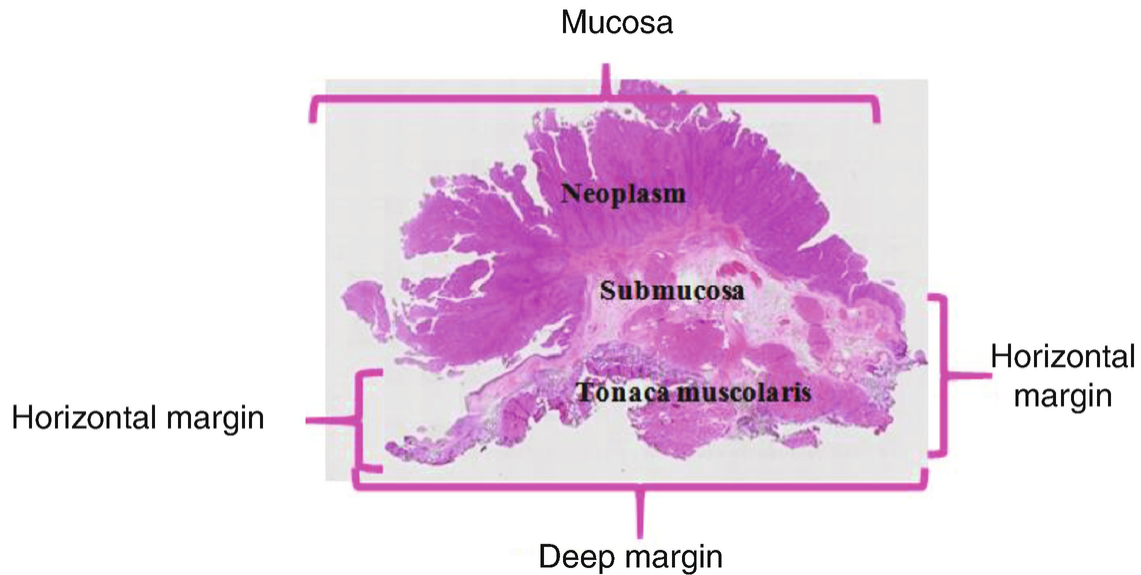


Fig. 3.3 Specimen obtained by ERBT: low-grade, non-invasive urothelial cell carcinoma

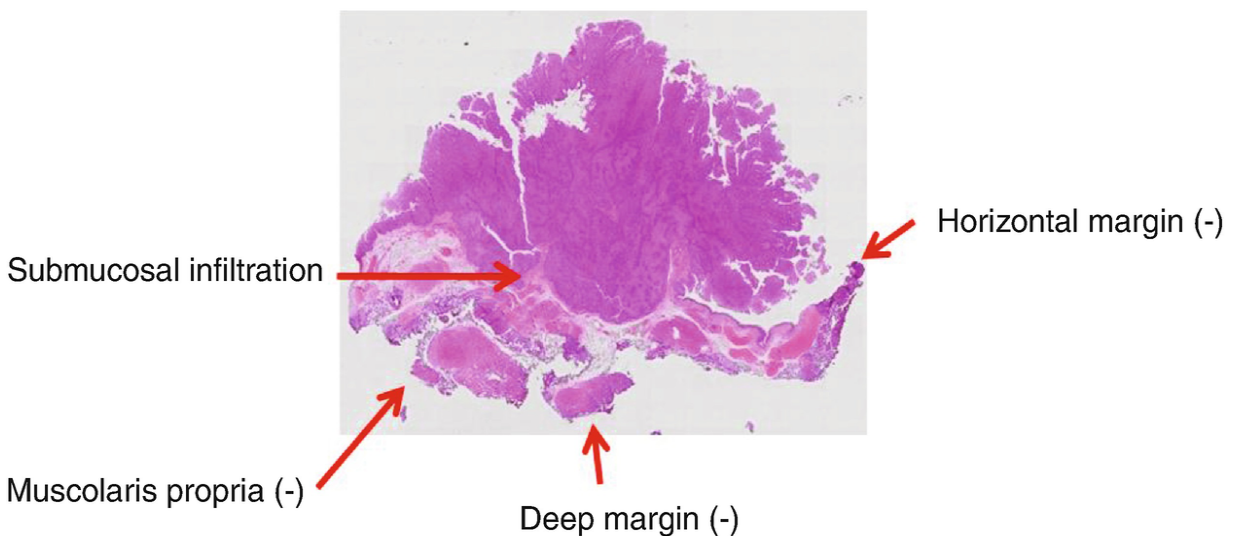


Fig. 3.4 Specimen obtained by ERBT: high grade, T1 urothelial cell carcinoma

The en-bloc technique has been described since 1997, but is still not used as often as it could since it is a procedure that requires certain conditions to be performed [21]. The size of the lesion is the primary limitation to the en-bloc approach. It is believed that tumors bigger than 3 cm cannot be retrieved in a single piece due to the urethral caliber restriction. The need for fragmentation of bigger tumor would increase the risk of tumor seeding, partially invalidating the procedure. Different instruments have been studied to improve specimen retrieval but there is still no systematic analysis of the issue.

Tumor location may pose another limitation in the application of ERBT, lesions localized in the posterior and anterior bladder wall and on bladder neck need virtually always to be resected with the conventional TURB.

The Technique

The instruments needed to perform ERBT are:

- A 0° direction of view endoscope with a working channel for morcellators up to 5 mm diameter
- A 5 mm grasping laparoscopic forceps
- A Collins loop

The procedure begins as a conventional TURB by positioning the nephroscope and localizing the lesions to be removed. Once it is assessed whether the size is suitable for en-bloc resection the lesion contouring can start. It is important to resect keeping a safe margin of apparently “normal” mucosa surrounding the base of the lesion (Fig. 3.5).

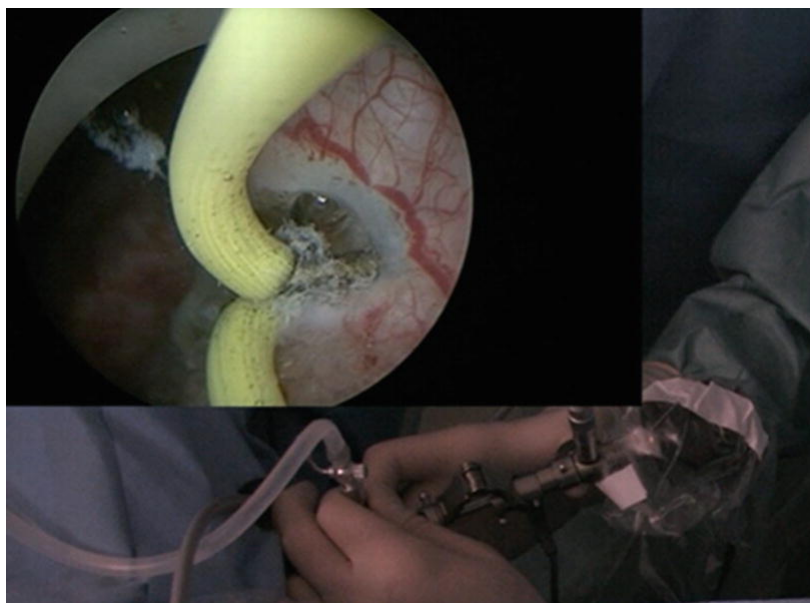


Fig. 3.5 Contouring of the lesion with Collins loop

Then the resection should be extended as deep as to reach the muscularis propria to achieve the correct staging [22, 23].

After the lesion has been detached from underlying tissue, the specimen is retrieved with a 5-mm forceps till the tip of the working channel and then collected with the instruments under vision.

Kramer et al. showed in a multicentric that all energy device (lasers, electric cautery) have been used to perform ERBT with comparable peri-operative and oncological results, making ERBT always feasible regardless the instruments disposable [24].

To date, ERBT is still a promising surgical approach with features that address the limitations of TURB.

There is growing evidence that ERBT improves the quality of the resected specimens and some results indicate that residual tumour in the second resection may be found in lower percentages. It also seems that TURB and ERBT do not differ significantly regarding peri-operative morbidity.

These findings strongly advocate for randomized controlled trials to be performed.

Highlights

- Too often TURB is not considered as a “simple” operation, often done by improperly trained surgeons. A specific teaching program, consisted in the presence of a consultant physician during all TURB performed by residents, the institution of a video-TURB archive for revisions, and weekly multidisciplinary discussion meetings between urologists and genito-urinary pathologist may significantly contribute to perform a “Good Quality TURB”.
- ERBT may help to overcome the most important limits of classical TURB: risk of tumor seeding, incomplete resection, thermal damage of specimen’s margin, and, above all, the absence of DM.
- It requires specific instrumentation and dedicated surgeon.
- There is growing evidence that ERBT improves the quality of the resected specimens.
- TURB and ERBT do not differ significantly regarding peri-operative morbidity.

Conclusions

ERBT is a growing surgical approach that has shown to the quality of the resected specimens and decrease the incidence of residual tumour at RETURB. ERBT is safe and doesn’t increase the risk of peri-operative complications compared to TURB.

Many studies are concordant on the safety and efficacy of ERBT therefore, while waiting for randomized study to be performed, we suggest TURB to be performed when possible with the en-bloc technique.

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4. Active Surveillance for Low-Risk Non-Muscle Invasive Bladder Cancer

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Keywords Active surveillance – Low-risk non-muscle invasive bladder cancer

Active Surveillance (AS) is an accepted policy in several low-risk malignancies, such as prostate cancer, small renal tumours, and in clinical stage I seminomatous germ cell tumours [1–5].

Regarding Bladder Cancer (BC), Non Muscle Invasive Bladder Cancer (NMIBC) accounts for ~50% of newly diagnosed cancers; although an high percentage of local recurrence has been reported in literature, only a small number of patients will progress to Muscle Invasive Bladder Cancer (MIBC) [6, 7]. Sylvester et al. reported a 5-year progression rate of pTa LG tumours of 0.8% and, even after recurrence, the chances of progressing to MIBC do not exceed 6% [8].

Particularly, patients with low-risk BC, defined as a pTa Low Grade (LG) papillary tumour, have a high risk of recurrence, but a very low risk of progression [8, 9]. The risk of recurrence is 15–61% and 31–78% after 1 year and 5 years, respectively; with a risk of progression of 1% after both 1 and 5 years [8].

Moreover, nevertheless Trans-Urethral Resection of Bladder (TURB) is considered the standard treatment for NMIBC, it is still an operation often requiring general anesthesia, executed in old patients, often with several and important comorbidities.

Additionally, the complications such as bleeding, bladder perforations or urethral strictures may become a significant problem in these patients.

Finally, the higher the number of repeated procedures, the higher the complication rates and the costs related to hospital stays and patient management.

In this context, in 2003, Soloway et al. suggested an AS program as a safe and valid alternative strategy to TURB [7]. They reported that only three patients (9%) progressed in either stage or grade, but none progressed to stage T2 disease within a mean period of 10 months. The authors found that the tumour growth rate was very slow, corresponding to 1.77 mm/month. This observation prompted other groups to investigate the role of observation for NMIBC.

To date, eight studies on AS have been published with a an overall number of patients enrolled in AS programs of 404 [7, 10–17]. Only four of these 404 patients (1%) showed progression to MIBC. Those patients were all T1/Grade 2 and did not undergo re-TURB. Three of the studies consists in abstracts presented at major urological meetings. The studies by Hernandez et al. and by de la Pena et al. follow the same series of patients over different time scales [13, 14, 16].

All the information reported in literature suggests the importance of re-TURB in patients with T1/Grade 2 when they are considered eligible for AS. There was grade and stage progression in 65 (14.4%) and 46 (10.2%) individuals, respectively (Table 4.1) Hurle and Coll have recently published the mid-term results from the **BIAS** (BIAS: Bladder cancer Italian Active Surveillance) Project, whose primary outcome was the check of adherence to AS its self [17]. This is a prospective study enrolling patients with history of pathologically confirmed low grade pTa–pT1a NMIBC and diagnosed with a tumour recurrence. The inclusion and exclusion criteria and the criteria for intervention are reported in (Table 4.2).

Table 4.1 AS studies

Reference	Patients/observations	Median time on observation, months	Pathological findings before observation	Grade progression n (%) or n/N	Stage progression n (%) or n/N	Progression to MIBC, n (%)	Total patients in study vs. total population n/N (%)
Soloway [7]	32/44	10.9	Ta/T1 Grade 1/Grade 3	3 (9.3)	2 (6.2)	0	NA
Martinez Caceres [10]	13/15	13.5	Ta/T1 Grade 1/Grade 3	2 (15.4)	3(2.31)	0	13/112 (11.6)
Gofrit [11]	31/43	15.3	Ta Grade 1/Grade 3	1 (2.32)	1(2.32)	0	NA
Pruthi [12]	22/32	23	Ta/T1 Grade 1/Grade 3	1 (4.5)	2(9)	0	22/173 (12.7)
Hernandez [13]	64/70	10.3	Ta/T1 Grade 1/Grade 3	5 (7.5)	11 (17.2)	0	64/273 (23.44)
De la Pena et al.[14]	156/211	13.7	Ta/T1 Grade 1/Grade 2	17 (10.9)	17 (30.9)	0	NA

Reference	Patients/observations	Median time on observation, months	Pathological findings before observation	Grade progression n (%) or n/N	Stage progression n (%) or n/N	Progression to MIBC, n (%)	Total patients in study vs. total population n/N (%)
Lozano [15]	68/NA	25	Papillary Urothelial Neoplasm of Lower Malignant Potential (PUNLMP) Ta/T1a Low Grade	3 (2.04)	4 (2.72)	0	NA
Hernandez [16]	186/252	13.6	Ta/T1 Grade 1/Grade 2	39 (20.7)	25 (13.6)	4 (2.15)	NA
Hurle [17]	55/70	12.5	Ta/T1 Grade 1/Grade 2	10 (18)	6 (10.9)	0	55/293 (19)
Hurle Update Series (EAU 2017)	99/120	21.3	Ta/T1 Grade 1/Grade 2	16 (16.2)	9 (9,1)	0	NA
Total	451	17.5	NA	65 (14.4)	46 (10.2)	4 (0.9)	NS

NA not applicable

Table 4.2 Inclusion and exclusion criteria and criteria for intervention

Intervention criteria	Exclusion criteria	Inclusion criteria
1. Progression in number of lesions 2. Progression in dimension of lesion/s 3. Positive urinary cytology 4. Persistent gross haematuria 5. Any further intervention (resection or electro-fulguration)	1. History of a high-grade carcinoma (Grade 3) 2. History of Carcinoma In Situ (CIS) 3. Positive cytology	1. Negative urine cytology 2. Presence of ≤ 5 lesions with a diameter of ≤ 10 mm 3. Absence of CIS 4. Absence of persistent gross haematuria

Follow-up assessment consisted of cytology and an in-office flexible cystoscopy every 3 months for the first year, and then every 6 months annually. Cystoscopy was performed under the supervision of an experienced urologist. Pathological evaluation of each case was reviewed by a single experienced uro-pathologist.

An update of this series, recently presented at European Association of Urology in 2017 reported that patients remained under AS for a median time of 21.3 months (Inter Quartile Range IQR: 21.5); 5 (5.05%) patients were lost to follow-up due to deaths, which were not related to BC. A failure was observed in 40 (40.4%) patients, corresponding to 45 events (37.5%). Within failure events, 17 (37.8%) were due to dimensions, 10 (22.2%) to number and three to contemporary dimension and number increase. Gross haematuria was the cause of failure in 10 events and positive cytology in five. Sixteen patients

experienced grade progression and 9 patients stage progression to pT1. Eleven failures presented as pT1a and 31 as pTa; six failures were classified as G3, 9 as G2 and 27 as G1. In three patients the TURB did not reveal neoplasm in pathological samples. One (1%) patient showed CIS. The overall adherence to the follow-up schedule was 95%.

The authors concluded AS for NMIBC as a reasonable option in patients with small, low stage, low-grade recurrent papillary BC after TURB. Although the current population is one of the largest with a long-term follow-up, further multicentre studies under randomisation criteria are mandatory in order to include AS in our daily practice. AS protocol for NMIBC could be a reasonable option in a select group of patients with small, recurrent BC.

Highlights

AS might be a reasonable strategy in patients presenting with small low-grade pTa/pT1a recurrent papillary bladder tumours. Risks of stage and grade progression are acceptable. AS reduces the number of interventions patients will need over a lifetime and avoids therapy induced complications.

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Part II

Non-muscle Invasive Bladder Cancer

5. How Good Are We at Predicting Outcomes in Non-Muscle Invasive Bladder Cancer?

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Keywords Non-muscle invasive bladder cancer – Prognosis – Prediction – Patient outcome – Recurrence – Progression

Introduction

Individual patient outcome depends on several different factors including the accuracy of the diagnosis, the quality of the transurethral resection of the bladder tumor (TURBT), the patient's clinical and pathological characteristics, and the treatment received.

Unfortunately, the diagnosis of non-muscle invasive bladder cancer (NMIBC) is subject to discrepancies in tumor stage and grade, both within the same pathologist and between pathologists [1, 2], leading to the possible misclassification of a patient's risk of recurrence or progression and an under- or an over-treatment. In a recent systematic review comparing the prognostic importance and the reproducibility and repeatability of the 1973 and 2004 WHO grading classification systems, it was concluded that the inter and intra observer variability of both grading systems was suboptimal [1].

In a review of seven studies carried out by the European Organization for Research and Treatment of Cancer (EORTC), the percent of patients with a recurrence at the first follow up cystoscopy after TURBT varied substantially between institutions and could not be explained by the patient's prognostic factors, suggesting that the incidence of residual tumor and the quality of the TURBT varied across institutions and surgeons [3]. The likelihood that muscle-invasive disease is detected by a second resection of initially T1 tumors ranges from 4% to 25% and increases to 45% if there is no muscle in the initial resection [4, 5]. Hence the quality of the TURBT is one of the most important factors in determining patient outcome.

Prognostic and prediction tools in bladder cancer is a topic which has received considerable attention [6]. Being able to accurately predict a NMIBC patient's risk of recurrence and progression to muscle invasive disease is important for choosing the most appropriate treatment after TURBT, whether this be a re-TURBT, a single immediate post TURBT instillation of chemotherapy, further intravesical instillations with either chemotherapy or bacillus Calmette-Guerin (BCG), or an early or even an immediate cystectomy. Likewise, prognosis is important for scheduling the frequency and duration of the follow up.

This chapter will review several of the tools that are available to predict a NMIBC patient's outcome after TURBT in an effort to answer the question: how good are we at predicting outcomes in non-muscle invasive bladder cancer?

Predicting Outcome in Individual NMIBC Patients

European Association of Urology Guidelines

European Association of Urology (EAU) treatment recommendations stratify patients into three groups of low, intermediate and high risk disease [4, 5]. Low risk patients are those with a single, primary, Ta, low grade/G1 tumor <3 cm in diameter without CIS. At the other extreme, high risk patients have any of the following tumor characteristics: T1, high grade/G3, CIS, or multiple and recurrent TaG1G2 tumors >3 cm. T1G3/HG patients with either CIS in the bladder or prostatic urethra, or with recurrent and/or

multiple and/or large tumors are considered to be the highest risk patients, as are patients who have failed BCG or have lympho-vascular invasion or an unusual variant histology of urothelial carcinoma [4, 5].

EORTC Risk Tables

The EAU stratification was developed using the 2006 EORTC's risk tables for predicting the short-term and the long-term risks of disease recurrence and progression in individual patients [7]. The EORTC scoring system is based on seven studies with more than 2500 patients, of whom 72% received intravesical chemotherapy, 6% BCG but without maintenance, and 22% received no intravesical instillations. The EORTC risk tables include the number of tumors, tumor size, prior recurrence rate, T category, 1973 WHO tumor grade and the presence of concurrent carcinoma in situ (CIS). Probabilities of recurrence varied from 15 to 61% at 1 year and from 31 to 78% at 5 years, while probabilities of progression varied from .2% to 17% and from .8% to 45% at 1 and 5 years, respectively (Table 5.1). One hundred eighty-one of 2070 (8.7%) patients without a recurrence at the first follow up cystoscopy at three months progressed compared to 80 of 313 patients (25.6%) with a recurrence at 3 months.

Table 5.1 Probabilities of recurrence and progression by risk group

	Recurrence probability			Progression probability		
	Group	1 Year	5 Years	Group	1 Year	5 Years
EORTC 2006 [7]						
Lowest risk	Recurrence score 0	0.15	0.31	Progression score 0	0.002	0.008
Highest risk	Recurrence score 10–17	0.61	0.78	Progression score 14–23	0.17	0.45
CUETO 2009 [8]						
Lowest risk	Recurrence score 0–4	0.08	0.21	Progression score 0–4	0.01	0.04
Highest risk	Recurrence score 10–16	0.42	0.68	Progression score 10–14	0.14	0.34
EORTC 2016 [9]						
Lowest risk	Prior recurrence rate $\leq$ 1/year and < 4 tumors	0.16 ^a	0.31 ^a	TaG1	0.003	0.02

	Recurrence probability			Progression probability		
	Group	1 Year	5 Years	Group	1 Year	5 Years
Highest risk	Prior recurrence rate > 1/year and ≥ 4 tumors	0.64 ^a	0.89 ^a	T1G3	0.11	0.19

^aApproximate probabilities

CUETO Scoring Model

In 2009, the Club Urologico Espanol de Tratamiento Oncologico (CUETO) developed a scoring model based on 1062 patients which predicted the short-term and the long-term risks of recurrence and progression in individual patients who were treated with 12 instillations of BCG during 5–6 months [8]. Their model differed from that of the EORTC in that it took into account patient age and gender, but not tumor size. Probabilities of recurrence varied from 8 to 42% at 1 year and from 21 to 68% at 5 years, while probabilities of progression varied from 1 to 14% and from 4 to 34% at 1 and 5 years, respectively (Table 5.1).

EORTC Nomograms and Risk Groups

In 2016, the EORTC published nomograms and risk groups for predicting early recurrence at 3 months, recurrence after 3 months, progression, disease specific and overall survival in patients receiving 1–3 years of maintenance BCG [9]. Taking into account the prior recurrence rate, number of tumors and 1973 WHO grade, the probability of recurrence at 3 months varied from 5 to 40%. In patients who were tumor free at 3 months, the probability of recurrence at 1 year varied from 11 to 31% while the probability of recurrence at 5 years varied from 26% to 55%. The probabilities of progression in the TaG1 patients and the T1G3 patients were 0.3% and 11%, respectively, at 1 year, and 2% and 19%, respectively, at 5 years (Table 5.1).

Limitations and Discrepancies of the EORTC and the CUETO Models

The EORTC and CUETO models have a number of limitations:

1. Very few patients had CIS.

2. The models are based on patients diagnosed and treated in the 1980s and 1990s. Many patients were under treated by today's standards, especially the high-risk patients who did not have a re-TURBT. In addition, the high-risk patients in the two earliest studies [7, 8] did not receive the currently recommended minimum of 1 year of treatment with maintenance BCG. Hence recurrence and progression rates in these series are likely to be higher than those found in current clinical practice.
3. The probabilities of recurrence and progression in the best prognosis and worst prognosis groups differed between the models (Table 5.1).

Applying the EORTC model to their data, CUETO found that although the EORTC risk tables provided adequate discrimination between patients with different prognoses, their calibration was poor. The EORTC model over-estimated the risks of recurrence and the risk of progression in the EORTC high risk category [10].

When the EORTC applied the CUETO model to their data, the CUETO model did not perform as well. Model discrimination, as measured by the C-index, decreased for both recurrence and progression. In addition, the CUETO model underestimated the risk of recurrence in good risk patients and overestimated the risk of progression at 5 years in high risk patients [9].

These differences have been attributed to differences in the efficacy of the treatments that the patients received in these series. The differences are largely consistent with the better efficacy of (maintenance) BCG.

Predicting Progression on Maintenance BCG

The question of how accurately we can predict progression in patients receiving maintenance BCG is of major importance. This is best assessed by calculating the negative predictive value (NPV) and the positive predictive value (PPV):

NPV = probability the patient does not progress if they are classified at low risk of progression.

PPV = probability the patient does progress if they are classified at high risk of progression.

In the 2016 paper from the EORTC [9], 501 of 523 TaG1 patients did not progress, so the negative predictive value in these patients was 96%. On the other hand, the positive predictive value in the T1G3 patients was only 19% (64 of 333 patients progressed) (Table 5.2). Although we can accurately identify the patients who do not progress (NPV = 96% in TaG1 patients), we cannot accurately identify the patients who will progress (PPV < 20% in T1G3 patients). More generally, similar results have been seen in the original EORTC study and in the CUETO study (Table 5.2) [11].

Table 5.2 Negative and positive predictive values for progression by risk group

	Negative predictive value		Positive predictive value	
	Group		Group	
EORTC 2006 [7]				
Lowest risk	Progression score 0	425/431 (98.6%)	Progression score 0	–
Highest risk	Progression score 14–23	–	Progression score 14–23	49/119 (41.2%)
CUETO 2009 [8]				
Lowest risk	Progression score 0–4	416/437(95.2%)	Progression score 0–4	–
Highest risk	Progression score 10–14		Progression score 10–14	28/90 (31.1%)
EORTC 2016 [9]				
Lowest risk	TaG1	501/523 (95.8%)	TaG1	–
Highest risk	T1G3	–	T1G3	64/333 (19.2%)

Which T1G3 Patients Treated with BCG Progress?

In a large retrospective multicenter study of 2451 T1G3 patients who received BCG as their initial treatment for T1G3 tumors (38% of whom received maintenance BCG), the overall progression rate at 10 years was 23%, but varied by subgroup from 17 to 52% [12]. The subgroup of patients ≥ 70 years with tumor size ≥ 3 cm and concomitant CIS had a progression rate of 52% at 10 years.

In another study, female gender and CIS in the prostatic urethra were found to be the most important prognostic factors for progression in T1G3 patients treated with induction BCG [13].

How Can We Improve the Prediction of Progression in T1G3/HG Patients?

We need to be able to better predict which T1G3/HG patients will progress despite “optimal” diagnosis, treatment and follow up. The models from the EORTC and CUETO do not take into account potential prognostic factors such as:

- Depth of lamina propria invasion (T1a, T1b, T1c)
- Tumor stage at re-TURBT
- Recurrence at 3 months
- CIS in the prostatic urethra
- Histological variants of urothelial carcinoma such as micropapillary
- Lympho-vascular invasion
- Molecular markers

Many promising molecular markers have been published. For example, molecular grade (FGFR3/MIB-1) has been shown to increase the predictive accuracy of the EORTC risk scores for progression [14]. Likewise, a promising five-gene expression signature to predict progression in T1G3 bladder cancer without CIS has recently been proposed [15]. However, none of the potential molecular markers have been sufficiently validated for use in every day clinical practice. To be useful in the clinic, one must determine whether the addition of molecular markers to the current prognostic models based on clinical and pathologic factors increases their predictive accuracy and the PPV, especially in the high-risk patients.

Further improvements in risk stratification to guide patient treatment may well be based on molecular markers, but we are not there yet.

Discussion

We can improve patient outcome if patients are diagnosed and treated in accordance with current clinical guidelines [4, 5]. However, long-term follow-up is not available for patients treated according to the current EAU

guidelines, so the degree by which the EORTC and CUETO scoring systems overestimate the risks of recurrence and progression in current clinical practice remains unknown. Long-term follow-up is needed, but by the time it is available, treatment practices may have already changed, thus making it difficult to validate new scoring systems for use in current-day clinical practice.

We can accurately identify those NMIBC patients who are unlikely to progress. However, the accurate identification of which NMIBC patients will progress to muscle-invasive disease is still a major problem. The positive predictive value of current models to identify high risk patients who do progress is woefully inadequate.

Because NMIBC patients who progress have a very poor prognosis, identification of factors that significantly increase our ability to identify, at an early stage, patients who will progress on intravesical treatment should be a top research priority.

Molecular markers have been proposed as a way of providing new, potentially important information related to the biology of the disease and patient prognosis, eventually leading to the development of more effective, individualized patient therapies. However, more research is needed to identify and validate molecular markers that improve the predictive accuracy and the positive predictive value of the currently available prognostic models.

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6. Adjuvant Treatment: Old and New Immunotherapy in Non-Muscle-Invasive Bladder Cancer

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Keywords BCG – Immunotherapy – Non-muscle invasive bladder cancer – Gene therapy – Oncovirus

Introduction

The treatment of bladder cancer (BC) has experienced a dramatic evolution; nevertheless, no significantly reduction in overall mortality has been reported over the past 20 years [1]. Against the background of this lack of significant improvement in BC prognosis, immunotherapy probably represents the most interesting field for exploration in BC research.

Immunotherapy is not a modern concept. It arose in nineteenth century when injection of *Streptococcus pyogenes* and *Serratia marcescens* directly into neoplastic tissue was observed to induce tumour regression in patients with a variety of neoplasms [2]. Unfortunately, the exact mechanism of action was far from being understood at the time. As a consequence, the

scientific community focussed its attention on other therapeutic fields, like chemotherapy and radiation therapy [3].

Nowadays it is well recognized that immunotherapy plays its role by helping the immune system to protect the body from foreign invaders, including cancer cells. Malignant cells express a different antigenic pattern compared with normal tissue, which can help the host immune system to recognize and kill them [4]. However, cancer cells have developed a number of escape mechanisms, such as immune system deactivation by release of cytokines, which suppress the host immune system and allow tumour proliferation [5].

According to the current evidence, the development of immunotherapeutic agents able to deactivate the cancer's negative co-signalling pathway could strongly improve the available treatment strategies for BC.

BCG and Combined Therapies

Bacillus Calmette-Guérin (BCG) , a live attenuated form of *Mycobacterium bovis*, represented the first connection between BC and immunotherapy. The anti-cancer effect of BCG was observed in the 1950s in mice [6], while first investigations in humans took place 10 years later. Despite the not encouraging results in the treatment of some tumours (prostate, lung, colon, etc.), topical BCG showed a strong activity against BC. In 1976 the first use of intravesical BCG in the treatment of superficial BC was reported by Alvaro Morales [7]. The treatment strategy was based on the 6-weekly instillation schedule proposed by Morales himself.

Nowadays, the precise mechanism of action by which BCG exerts its therapeutic effects remains poorly understood [6]. Current research suggests that BCG probably acts by stimulating both an inflammatory tumour response and a primary innate immune response to clear residual BC cells [8]. According to Sapre et al., after its internalization, BCG induces release of several cytokines (including interferon and interleukins) and finally promotes the killing of cancer cells through a T-mediated cytotoxic reaction [9].

BCG still represents the gold standard treatment for high-risk non-muscle-invasive bladder cancer (NMIBC) [10]. Its administration decreases recurrences and delays progression. Despite this strong evidence, use of

intravesical BCG alone in high-risk NMIBC patients seems insufficient, especially in BCG non-responders.

To enhance its efficacy, combination of BCG with chemotherapeutic agents has been proposed. The rationale for this approach is based on the role of fibronectin, the molecule through which BCG binds tumour cells. The inflammatory reaction induced by chemotherapeutic agents like mitomycin C (MMC) should increase fibronectin exposure and consequently facilitate BCG attachment [11]. Solsona et al. compared the combination of BCG with MMC to BCG alone in a large cohort of high-/intermediate-risk NMIBC. The 5-year disease-free interval was significantly longer in the sequential arm compared with the BCG arm (20.6% and 30.9% respectively, $p = 0.003$) [12]. This improvement in BCG efficacy due to the combination with MMC had already been suggested by a randomized controlled trial comparing BCG alone with BCG plus electromotive MMC. Two hundred and twelve T1 patients were randomized into the above-mentioned treatment arms. During a median follow-up of 88 months the combination therapy resulted in a longer disease-free interval and lower progression and mortality rates compared with BCG alone [13].

It has been clearly demonstrated that instillations of BCG induce infiltration of the bladder wall by neutrophils, which play an important role in the antitumor effect of BCG itself [14]. Neutrophils can both exert a direct anticancer activity and stimulate the secretion of chemotactic agents, which increase the immune system response [15]. In order to stimulate the activation and the migration of neutrophils, a number of molecules are under investigation. According to the available literature the most encouraging results derive from interleukins (IL). IL-15 has already been studied as an antitumour agent. During inflammatory processes, IL-15 plays a crucial role in neutrophil activation and migration [16].

On the basis of all this evidence, the use of recombinant BCG strain expressing some interleukins has been proposed, with interesting results. A recombinant BCG + IL-15 was tested in mice by Takeuci et al. Compared with BCG alone, the recombinant BCG was able to suppress tumour growth and increase infiltration by neutrophils [17]. Similarly, the efficacy of a recombinant BCG with a mutated IL 15 (ALT 803) was assessed in a randomized study using mice. BCG plus ALT 803 led to a 46% decrease in tumour burden, compared with a 35% decrease for ALT alone and a 15% decrease for BCG alone. Moreover, the combination BCG plus ALT 803

was able to induce a unique lymphocytic infiltration, with a significant increase in natural killer cells [18].

Checkpoint Inhibitors: PD-1, PD-L1, CTLA4

Immune T cells activate a signalling pathway, which results in the destruction of malignant cells. These mechanisms can be evaded by the expression of surface molecules that interact with the receptors on T cells. The final result is inactivation of the host immune system and consequently proliferation of tumour cells. Because of their role, these molecules and their receptors on T cells are globally called checkpoint proteins [19]. Logically, the use of checkpoint inhibitors should prevent inactivation of the host immune response by tumour cells. Three checkpoint molecules, programmed cell death protein-1 (PD-1), programmed death ligand-1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), have been already investigated in the treatment of BC, and have inhibitor agents either approved or in late-stage development [3]. The available literature suggests a possible correlation between the level of checkpoint inhibitors and BC aggressiveness. Specifically, it has been found that higher levels of PD-L1 on tumour cells are associated with high-grade tumours, and with a worse prognosis [20]. As a consequence this subgroup of cancers should be the best responder to a checkpoint blockade.

The first report of the use of checkpoint inhibitors in BC therapy was published in 2014 [21]. Since then a number of monoclonal antibodies (Ab) have been developed to inhibit the checkpoint proteins. PD-L1 inhibitors include atezolizumab, durvalumab and avelumab. Agents that inhibit PD-1 are nivolumab and pembrolizumab, while ipilimumab and tremelimumab are two agents that block the activities of CTLA-4.

The first Ab found to be active in the treatment of BC was atezolizumab. It is currently the only PD-L1 inhibitor specifically approved for patients with locally advanced or metastatic urothelial carcinoma, who have experienced disease progression on or after platinum-based chemotherapy. In a cohort of 310 patients with advanced or metastatic urothelial carcinoma and already treated with a platinum-based CT, the use of this monoclonal Ab resulted in an objective response rate (ORR) ranging between 16 and 28% (in high-level PD-L1 tumours) during a mean follow-up of 1.5 years. Moreover, responding patients presented a durable response

with a median duration not reached after 17.5 months. Nausea and fatigue were the most common adverse events [22].

Nivolumab was the first PD-1 inhibitor approved and is now used as second-line therapy for advanced/metastatic urothelial carcinoma. An ORR of 24% was observed in patients with metastatic urothelial carcinoma and PD-L1 expression <1%, and the median overall survival was 9.7 months [23]. Pembrolizumab is another approved PD-1 inhibitor. In the KEYNOTE-012 trial, pembrolizumab second-line therapy conferred an ORR of 25% and the 12-month progression-free survival (PFS) rate was 19% in a group of patients with advanced urothelial carcinoma [24]. In a subsequent study this Ab was used as first-line therapy in patients with advanced/inoperable urothelial cancer. The overall ORR was 24% while in patients with >10% combined positive score (CPS; tumour and immune cell PD-L1 expression) the ORR reached 36.7% [25].

Viral Gene Therapy and Cancer Vaccines (Intravesical Oncoviral Therapy)

New fields are under investigation to find alternative treatment options for BCG non-responders. Gene therapy is a promising and attractive strategy for cancer biotherapy and some authors have already pointed out the potential antitumor effect exerted by the intravesical application of oncoviruses.

Zhai et al. assessed the efficacy of an oncolytic adenovirus carrying the E1A androgen receptor. This recombinant adenovirus induced significant regression of tumour growth and markedly prolonged survival in tumour-bearing mice [26].

In 2012, intravesical viral therapy was applied in humans for the first time [27]. In this phase I clinical trial, a mutated oncolytic adenovirus was used (GC0070). The most interesting characteristic of this virus is its interaction with the retinoblastoma pathway, which is frequently deregulated in BC [28]. Thirty-five BCG-refractory patients were treated with intravesical administration of single- or multi-dose adenovirus. The overall response rate (defined as the absence of recurrence at cystoscopy with or without a pathology report) was 48.6%, with a better result in patients treated with the lowest dose [27].

Vicinium currently represents one of the new frontiers in conservative treatment for NMIBC. Vicinium is a single-chain anti-EpCAM (epithelial cell adhesion molecule) antibody fragment fused with a truncated fragment of *Pseudomonas* exotoxin A. Vicinium specifically targets and induces apoptosis in EpCAM-positive tumours. Twenty-three BCG-refractory or intolerant patients with CIS received Vicinium weekly for 6 weeks. Efficacy data showed a complete response in nine of the 23 patients at 3 months [29].

Conclusions

BCG is an effective immunotherapy and is still considered the gold standard treatment for NMIBC. However, there is a subgroup of patients who will not respond to BCG and have a higher risk of subsequent recurrence and progression. In order to improve its efficacy, a number of combinations of BCG with other agents have been proposed but they still need to be consolidated. In this framework, immunotherapy, especially with checkpoint inhibitors, will play a crucial role in improving the NMIBC response rates to conservative treatment.

Currently, gene therapy and anticancer vaccines are among the greatest challenges in BC research but their clinical application remains very far away.

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7. The Role of New Experimental Conservative Therapies for High Risk Non-Muscle Invasive Bladder Cancer: Could We Trust Them?

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Keywords Non-muscle invasive bladder cancer – Intravesical immunotherapy – BCG failure – Electromotive drug administration – Chemo-hyperthermia

Introduction

For decades, intravesical chemotherapy and immunotherapy with Bacillus Calmette-Guerin (BCG) have represented the only adjuvant treatment for reducing the risk of recurrence and progression in high-grade (HG) non-muscle invasive bladder cancer (NMIBC). BCG seems to be the most effective intravesical agent for preventing NMIBC recurrence and, in certain amount, progression [1]. Nevertheless, even after BCG, up to 40–50% of patients will eventually recur [2]. There is, therefore, an unmet need

to find new adjuvant therapies, or at least to improve the existing ones. In the last years, several new device-assisted therapies have been developed with the aim to improve the effectiveness of intravesical chemotherapy by increasing its penetration into the bladder wall. Among these, electromotive Drug Administration (EMDA) and chemo-hyperthermia (CHT) are the most investigated, and those supported by a certain level of evidence. According to the last European Association of Urology Guidelines, however, these device-assisted therapies are not recommended as first-line adjuvant treatment for NMIBC. Their use can be taken into consideration only in selected cases of BCG failures not willing or not suitable to radical cystectomy. Up-to-date, in fact, these treatments have been considered inferior to radical cystectomy, also due to the low level of evidence of published studies [3].

Electromotive Drug Administration (EMDA)

Mitomycin C (MMC) is one of the most widely used chemotherapeutics agent in low/intermediate risk NMIBC. Accordingly to the international guidelines the treatment schedule consists in one early postoperative instillation eventually followed, based on final pathology, by six weekly instillations. Usually MMC is instilled in bladder by indwelling catheter. Changes in intravesical ions, urinary osmolality and pH influence the urothelial permeability, modifying drug penetration into the bladder wall. It has been observed that recruitment of electrokinetic forces accelerates drug administration rates across biologic membranes [4]. The term “electromotive drug administration” (EMDA) refers to the transport of all water-soluble drugs under the influence of an electric field. The iontophoresis seems to be the principal physical mechanism involved in EMDA [5]. Intravesical chemotherapy administration by EMDA is widely studied in bladder cancer (BC) since the ‘90s.

Supporting Data

Di Stasi et al. firstly evaluated the effectiveness of MMC EMDA vs. MMC passive diffusion (PD) and vs. BCG in high risk NMIBC. In this study, a comparable percentage of complete responder at 3 and 6 months for MMC-EMDA and BCG was found. Moreover, no differences between the tree

groups in term of progression rate and overall survival (OS) were reported [6].

Subsequently the same group performed a trial evaluating the effectiveness of BCG plus MMC-EMDA vs. BCG alone for high risk NMIBC: a higher disease free interval, a lower progression rate, a lower overall mortality and disease specific mortality in the combination therapy group was reported [7]. These encouraging results were successively confirmed in a recent published single arm trial (schedule: BCG at week one and two followed by one EMDA-MMC repeated three times) [8].

The efficacy of EMDA was evaluated also in the preoperative setting. Di Stasi et al. evaluated the effectiveness of pre-TURBT EMDA MMC for newly diagnosed BC (randomized TURBT alone, single post TURBT MMC and EMDA MMC pre TURBT). They found a longer disease-free survival and a lower recurrence rate ($p < 0.001$) in intermediate and high-risk patients treated with pre TURBT EMDA-MMC. No differences in term of overall survival were reported [9].

Safety and Tolerability

In the reported series, the rate of EMDA-related adverse events (AEs) did not differ from those of standard intravesical chemotherapy or immunotherapy. The most common reported AEs were bladder spasms and pain, followed by dysuria, frequency/urgency and hematuria.

Three cases of severe toxicity due to allergic reaction to MMC during EMDA were reported [6]. On the pre-TURB EMDA trial Di Stasi et al. reported no differences between the study groups in term of AEs, they did not show differences in TURB complications in EMDA group [9].

Conversely, when administered in combination with BCG, a surprisingly high rate of treatment interruption was reported (AEs rate = 28%) [8].

Chemo-hyperthermia

Hyperthermia (HT) is today used in the treatment of several human cancers [10–12]. The cellular effects of HT can be divided into three categories: direct cells toxicity, angiogenesis inhibition and synergisms with chemotherapy.

Different devices for intravesical HT have been developed. Usually, MMC is instilled into the bladder by a specific indwelling catheter and

different devices allow intravesical HT (41–44 °C).

Supporting Data

CHT with MMC has been mostly proposed as adjuvant treatment in order to reduce the probability of recurrence and progression in NMIBC, especially in patients who failed BCG therapy. In the majority of studies regarding intravesical CHT, HT is provided by the Synergo[®] device (Medical Enterprises, Amsterdam, The Netherlands). Synergo system provides HT directly irradiating the urothelium and bladder wall through a 915-MHz microwave applicator and allows the continuous circulation of MMC through a 20-Ch three-way catheter and a peristaltic pump. The target temperature is set between 41 and 44 °C. The treatment usually consists of an induction cycle of 6 weekly instillations of MMC with HT, followed by a maintenance of monthly instillation for 1 year.

In one of the first published trials, Colombo et al. evaluated the efficacy of CHT vs. MMC alone in Ta-T1 stage NMIBC. CHT resulted more effective than chemotherapy alone, with reported recurrence rates of 17.1% and 57.5%, respectively [13]. The long-term efficacy results of that study have been reported in an update published in 2011; at a median follow-up of 90 months (6–154) recurrence was found in 14 patients of CHT group (40%) vs. 32 patients of chemotherapy group (80%), $p < 0.001$ [14].

Arends et al., in a large single center retrospective study of 160 patients (80.6% BCG failure) treated with CHT, found encouraging RFS rates (60% and 47% at 1 and 2 years, respectively) [15].

Gofrit et al. evaluated in a prospective trial the efficacy of CHT in high risk NMIBC. The RFS rate for the whole study was 71% after a median follow-up of 15.2 months. No cases of tumor progression occurred during follow-up. No significant difference was found between Ta or T1 tumors, BCG naive or BCG failure patients, numbers of previous occurrences [16]. These results in high-risk NMIBC patients were successively confirmed [16, 17]. CHT seems to be effective also in the treatment of CIS: in the study performed by Witjes et al., after a median follow up of 22 months (range 3–77) only 49% of patients had a recurrence. Moreover, no differences between patients who were or were not BCG failures were observed [18].

Recently, Arends et al. reported the results from a prospective trial evaluating CHT vs. BCG in high risk NMIBC after a follow up of

24 months: the RFS was higher in CHT group vs. BCG (81.8% vs. 64.8%, $p = 0.02$), in CIS patients the complete response rate did not differ between groups and no differences in progression rate were reported [19].

Safety and Tolerability

CHT appears to be burdened by a higher AEs rate compared to MMC alone, with a not negligible drop-out rate. AEs have been observed in a notable percentage of patients (till 60–70% in some series), even if of low grade in the majority of the cases. The most common reported AEs were bladder spasms and pain, followed by dysuria, frequency/urgency and hematuria. Arends et al. observed a more frequent occurrence of bladder spasm and pain during the treatment course (occurring in 23.3% and 16.8% of the patients, respectively), while dysuria and frequency/urgency usually came out after treatment (in 22.6% and 27.3% of the patients, respectively). In this series, 97% of events were of grade 1–2 [15]. One serious AE (grade 4) was reported: one patient underwent cystectomy for severe lower urinary tract symptoms (LUTS) after treatment cessation despite being tumor free [16]. However, the most common reported cause of treatment discontinuation is represented by an allergic reaction to MMC and only in a smaller percentage of cases by pain, frequency, dysuria or hematuria [20, 21].

Highlights

- Nowadays, conservative therapies for very high-risk NMIBC (CHT and EMDA) could represent a feasible and safe treatment, even if high-quality trials, thus producing good levels of evidences, are needed.
 - EMDA and CHT appear to have a good tolerability even if we should consider pain, frequency, dysuria or hematuria as common events.
 - Future studies should be focused on better identifying the categories of patients that could benefit from bladder conservative treatment.
- Moreover, randomized control trials comparing bladder-preserving therapy (EMDA CHT) vs. BCG as first line therapy in intermediate and high-risk NMIBC are warranted.

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Part III

Muscle Invasive Bladder Cancer

8. Is There Still a Role for Radical Cystectomy?

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Keywords Radical cystectomy – Lymph-node dissection – Outcomes – Orthotopic neobladder – Bladder sparing

Introduction

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, whilst it drops to 11th when both genders are considered [1]. In the European Union, the age-standardized incidence rate is 19.1 for men and 4.0 for women [2, 3]. Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, carcinoma in situ [CIS]) or submucosa (stage T1) while 25% is muscle invasive [1]. Tobacco smoking is the most well-established risk factor for BC, causing 50–65% of male cases and 20–30% of female cases [4].

Radical Cystectomy and Lymphadenectomy

Radical cystectomy is the standard treatment for localized MIBC in most Western countries [5, 6]. Recent interest in patients' quality of life (QoL) has promoted the trend toward bladder preserving treatment modalities, such as radio- and/or chemotherapy. Performance status (PS) and age

influence the choice of primary therapy, as well as the type of urinary diversion, with cystectomy being reserved for younger patients without concomitant disease and with a better PS. According to the EAU NMIBC Guidelines, RC is recommended for patients with MIBC T2-T4a, N0-Nx, M0 [6]. Other indications include high risk and recurrent superficial tumours, BCG-resistant Tis, T1G3, as well as extensive papillary disease that cannot be controlled with TURB and intravesical therapy alone.

Three types of diversion are currently used after RC: *incontinent or continent abdominal wall diversions* (ureterocutaneostomy, ileal or colonic conduit, continent pouches); *urethral diversion or neobladders*, provided the urethral margin is negative, and *rectosigmoid diversions* (such as uretero-(ileo-)rectostomy) [1].

Age alone is not a criterion for offering continent diversion. Comorbidity, cardiac and pulmonary function, and cognitive function, are all important factors that should be considered, along with the patient's social support and preference. Age >80 years is often considered to be the threshold after which neobladder reconstruction is not recommended. However, there is no exact age for a strict contraindication.

Orthotopic neobladder substitution and ileal conduit are by far the two most used diversions. Oncologic results after orthotopic neobladder or ileal conduit are similar in terms of local or distant metastasis recurrence, although secondary urethral tumours seem less common in patients with neobladder compared with an ileal conduit. Although gender should not be a selection criterion for neobladder substitution, large series from experienced centers still report more neobladder substitution in men (80%) compared with women (50%) Bowel preparation is no longer mandatory, and also the so-called fast-track measurements may reduce the time of bowel recovery and physical recovery. Contraindications for neobladders are debilitating neurologic and psychiatric illnesses, limited life expectancy, urethral tumour involvement, and impaired liver or renal function. Relative contraindications are high-dose preoperative RT, complex urethral stricture disease, severe urethral sphincter-related incontinence, and age >80 years.

Ureterocutaneostomy is on the contrary the simplest form of cutaneous diversion. It is preferred in older or compromised patients, especially in those with a single kidney. Technically, either one ureter, to which the other shorter one is attached end-to-side, is connected to the skin (transureteroureterocutaneostomy) or both ureters are directly anastomosed

to the skin. Due to the smaller diameter of the ureters, stoma stenosis has been observed more often than in intestinal stomas [1].

Salvage cystectomy is indicated in non-responders to conservative therapy, recurrence after bladder-sparing treatment, and non-urothelial carcinoma (these tumours respond poorly to chemotherapy and RT). It is also used as a purely palliative intervention, including for fistula formation, pain and recurrent visible macrohaematuria (palliative cystectomy) [1].

In men, standard RC includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional LNs [7]. Prostate-sparing cystectomy is an option in a subset of carefully selected patients with BC without involvement of the prostatic urethra and without prostate cancer. This procedure is oncologically safe with good functional results as long as it is performed in an experienced center [8]. In women, standard RC includes removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and LNs [9].

The clinical significance of lymphadenectomy is still controversial: some authors consider LND a staging procedure, while others consider it therapeutic. However, EAU guidelines suggest to perform a lymph node dissection as an integral part of cystectomy (GR A) [1].

Another controversial aspect is the extent of LND. It has not been established to date. *Standard* lymphadenectomy in BC patients involves removal of nodal tissue cranially up to the common iliac bifurcation, with the ureter being the medial border, and including the internal iliac, presacral, obturator fossa and external iliac nodes [10]. *Extended* lymphadenectomy includes all LNs in the region of the aortic bifurcation, and presacral and common iliac vessels medial to the crossing ureters. The lateral borders are the genitofemoral nerves, caudally the circumflex iliac vein, the lacunar ligament and the LN of Cloquet, as well as the area described for standard lymphadenectomy [10–14]. A *super-extended* lymphadenectomy extends cranially to the level of the inferior mesenteric artery [15, 16] (Fig. 8.1a, b).

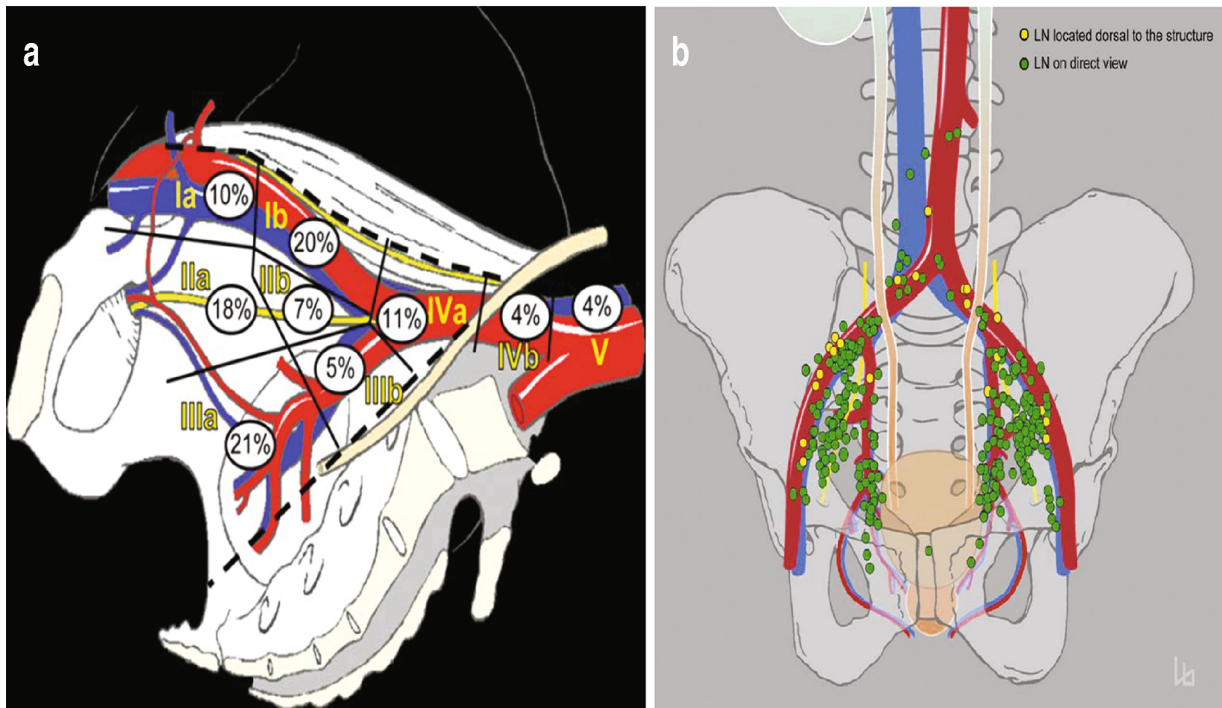


Fig. 8.1 (a) Boundaries of pelvic lymph node dissection subdivided into different regions and distribution of the technetium Tc99m–positive lymph nodes, used for the single-photon emission CT (SPECT): external iliac (Ia) distal and (Ib) proximal, obturator fossa (IIa) distal and (IIb) proximal, internal iliac (IIIa) distal and (IIIb) proximal, common iliac (IVa) distal and (IVb) proximal, (V) para-aortic/caval [22]. (b) Fusion image of the primary lymphatic landing sites transferred from three-dimensional (3D) data sets and superimposed into an idealized anterior-posterior projection of the pelvis [22]

It has been suggested that PFS (progression-free survival) as well as OS (overall survival) might be correlated with the number of LNs removed during surgery, although there are no data from RCTs on the minimum number of LNs that should be removed. Nevertheless, survival rates increase with the number of dissected LNs [17]. Removal of at least ten LNs has been postulated as sufficient for evaluation of LN status, as well as being beneficial for OS in retrospective studies [18–20].

Gschwend et al. reported recently the results of a prospective randomised study comparing limited vs. extended lymphadenectomy in patients with bladder cancer. Limited LND included six fields: obturator, internal, external iliac nodes. Extended LND included 14 fields: the previous 6 and the nodes of the deep obturator fossa, presacral, paracaval, inter-aortocaval and paraaortic up to the inferior mesenteric artery.

Neo-adjuvant chemotherapy or radiotherapy were excluded. Adjuvant chemotherapy was allowed.

Primary endpoint was recurrence free survival (RFS). Secondary endpoint was cancer specific survival (CSS). The planned total sample size was 400 patients to detect an improvement of 15% in recurrence free survival (from 50 to 65%) in the extended arm. From 2000 to 2006 437 patients were randomised but 375 were eligible. 191 patients received L-LND while 184 E-LND. Tumors were locally confined in 49.6% (pT1-T2 N0) while 50.4% were pT4. The median Number of LNs retrieved was 19 in the L-LND vs. 32 in the E-Arm. 24% of patients had positive nodes.

The 5-year RFS was 62% in L-LND vs. 69.3% in E-LND (not significant $p = 0.13$). The 5-year CSS was 66.2% in the L-LND vs. 77.5% in the E-LND arm (not significant $p = 0.13$). There was a trend but no significant difference toward improvement in RFS and CSS with E-LND was observed.

However, a subgroup analysis of pT2 patients (160 patients) was performed and a possible benefit in favour of E-LND was observed.

Complications: No difference in either 30 or 90-day major complications was seen (Clavien >3). Lymphoceles were observed in 9.3% of cases in E-Arm vs. 3.7% in the L-Arm ($p = 0.03$). The authors stressed that if E-LND confers a survival benefit it is likely that it is in the organ confined pT2 tumors [21].

In conclusion, extended LND might have a therapeutic benefit compared to less-extensive LND, but due to study bias, no firm conclusions can be drawn [21].

Neoadjuvant Chemotherapy

RC only provides 5-year survival in about 50% of patients [5, 23–26]. To improve these results, *neoadjuvant chemotherapy* (NAC) has been used since the 1980s [27, 28]. In the most recent meta-analysis, published in 2005 [29], with updated patient data from 11 randomised trials ($n = 3005$), a significant survival benefit was shown in favour of NAC. The results of this analysis confirmed the previously published data and showed a 5% absolute improvement in survival at 5 years. Data support to offer neoadjuvant chemotherapy (NAC) for T2-T4a, cN0M0 bladder cancer, always using cisplatin-based combination therapy. (GR A) [29]. The combination of 2–3 cycles of chemotherapy followed by RC with extended LND (>20 nodes)

should be considered nowadays the best possible treatment for patients with MIBC achieving the longest survival.

Sparing-Techniques

Functional results after RC are considered an important issue. Continence and potency are the major concerns. Different sparing-techniques have been described to improve voiding and sexual function in patients undergoing RC for BC. No consensus exists regarding which approach preserves function best [1]. Four main types of sexual-preserving techniques have been described:

1. *Prostate sparing cystectomy* : part or the whole prostate is preserved including seminal vesicles, vas deferens and neurovascular bundles.
2. *Capsule sparing cystectomy* : the capsule or peripheral part of the prostate is preserved with adenoma (including prostatic urethra) removed by TURP or en-bloc with bladder. Seminal vesicles, vas deferens and neurovascular bundles are also preserved.
3. *Seminal sparing cystectomy* : seminal vesicles, vas deferens and neurovascular bundles are preserved.
4. *Nerve sparing cystectomy* : the neurovascular bundles are the only tissue left in place.

The evidence base suggests that these procedures may yield better sexual outcomes than standard cystectomy without compromising oncological outcomes. However, the overall quality of the evidence is moderate, and hence if a sexual-preserving technique is offered, patients must be carefully selected, counselled and closely monitored [1, 30]. Patients selection is based on organ-confined disease, absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck and Cis (LE 2; GR A).

Controversy

The controversy remains on the indication of RC in MIBC:

- **Locally advanced tumours (T4b)**, invading the pelvic or abdominal wall): they may cause several debilitating symptoms, including bleeding, pain and urinary obstruction. These patients need palliative treatments, such as RT and/or palliative cystectomy with urinary diversion that should be considered mainly for symptom relief [31–33]
- **Age, RC and the type of urinary diversion.** Cystectomy is associated with the greatest risk reduction in disease-related and non-disease-related death in patients aged >80 years [34]. The largest, retrospective, single-institution study on cystectomy to date found that patients aged >80 years had increased post-operative morbidity, but not increased mortality. Although some patients successfully underwent a neobladder procedure, most patients were treated with an ileal conduit diversion [35]. It is particularly important to evaluate functioning and QoL of elderly patients using a standardized geriatric assessment, as well as carrying out a standard medical evaluation [36]. Above all in these patients, a multidisciplinary approach is a must to reduce complication rate.

RC in Elderly Patients: Is It the Best Choice in Octogenarians?

To evaluate if an aggressive approach is indicated it would be important to know:

1. *Life expectancy of an 80 y-old patient*
2. *What happens to the same patient with invasive bladder cancer if left untreated*



Answers:

1. Octogenarians are expected to live 6 to 8 years of active life
 2. The untreated patients with bladder cancer will die of their disease in 2 years
- QoL should also be always considered

The incidence of bladder cancer increases with advancing age. Considering the increasing life expectancy and the increasing proportion of elderly people in the general population, radical cystectomy will be considered for a growing number of elderly patients who suffer from muscle-invasive or recurrent bladder cancer [37].

Existing guidelines on management of MIBC do not preclude curative treatments for elderly patients. However, it is necessary to assess the risks and benefits of a treatment to avoid overtreatment that results in decreased health-related quality of life without prolonging survival [38].

EAU guidelines [1] underline to base the decision on bladder-sparing treatment or radical cystectomy in elderly/geriatric patients with invasive bladder cancer on tumour stage and comorbidity. (GR B) and to assess comorbidity by a validated score, such as the Charlson Comorbidity Index, while the American Society of Anesthesiologists (ASA) score should not be used in this setting.

Complications related to RC may be directly related to pre-existing comorbidity as well as the surgical procedure, bowel anastomosis, or urinary diversion. A significant body of literature has evaluated the usefulness of age as a prognostic factor for RC [39–41]. Advanced age has been identified as a risk factor for complications of RC, although chronological age is less important than biological age. Age carried the highest risk for other-cause mortality but not for increased cancer-specific death, while the stage of locally advanced tumour was the strongest predictor for decreased CSS [42]. Stratifying elderly patients according to their risk-benefit profile using a multidisciplinary approach will help to select patients most likely to benefit from radical surgery and to optimize treatment outcomes [37].

Recently, a long-term experience from two high Italian volume centers also supported the use of RC in octogenarians. In this study, authors retrospectively collected data of 1010 patients who received RC for infiltrative or recurrent high grade T1 TCC of the bladder from 2000 to 2012. 170/1010 patients (16.8%) were 80 years old or older. The mean follow-up was 44.5 months. The results of this study showed that 90 days mortality and complications were 8 and 40% respectively and that mayor complications were correlated with high ASA score (ASA 3–4), type of urinary diversion (Bricker) and surgical approach (intraperitoneal) [43].

Cystectomy in the elderly may be justified when life expectancy is greater than 2 years. Age alone should not defer octogenarians from a curative procedure

RC in MIBC: Oncological Results and 5–10 years Survival

According to a multi-institutional database of 888 consecutive patients undergoing RC for BC, the 5-year recurrence-free survival was 58% and the CSS was 66% [44].

Recurrence-free survival and OS in a large single-center study of 1054 patients was 68 and 66% at 5 years and 60 and 43%, at 10 years, respectively, for the entire cohort [5]. Specifically, in this study, the 5- and 10-year recurrence-free survival was 83% and 78% respectively for T1 tumors; 89% and 87% for T2, respectively; 78% and 76% for T3a. Patients with non-organ-confined (T3b, T4), lymph node-negative tumors demonstrated a significantly higher probability of recurrence compared with those with organ-confined bladder cancers ($p < 0.001$). The 5- and 10-year recurrence-free survival for T3b tumors was 62% and 61%, and for T4 tumors was 50% and 45%, respectively. The 5- and 10-year recurrence-free survival for patients with lymph node tumor involvement was 35%, and 34%, respectively, which was significantly lower than for patients without lymph node involvement (78% and 75% respectively, $p < .001$).

In other studies, the 5-year recurrence-free survival in node-positive patients who underwent cystectomy was considerably less at 34–43% [5, 45, 46].

Hautmann et al. published similarly long-term oncologic outcomes among 1100 patients who underwent RC; they exhibited an overall 10-year cancer-specific survival (CSS) rate of 67% [47].

Morbidity and Mortality

In three long-term studies, and one population-based cohort study, the peri-operative mortality was reported as 1.2–3.2% at 30 days and 2.3–8.0% at 90 days [23, 47–50]. In a large single-center series, early complications (within 3 months of surgery) were seen in 58% of patients [48]. Late morbidity was usually linked to the type of urinary diversion [51, 52]. In general, lower morbidity and (peri-operative) mortality have been observed

by surgeons and in hospitals with a higher case load and therefore more experience [49, 53, 54].

MIBC: The Goals of Radical Surgery

Debulking (removing the bladder with tumor and all the tissue in the pelvis together with the lymph-nodes) trying to have negative margins.

Preserving QoL

Continence when possible (according to disease stage) with prostate/gynecological sparing surgery and bladder reconstruction

Potency if indicated

Try to minimize complications

Prolong survival

Mini-Invasive RC: Options to Reduce Complications Rate

Robot-Assisted Radical Cystectomy (RARC)

In attempts to decrease the morbidity of the procedure, minimally invasive techniques have been employed for both the extirpative (i.e. radical cystectomy, extended lymph node dissection) as well as the reconstructive time of the procedure. Current laparoscopic and robotic-assisted techniques allow for the performance of these procedures in selected patients with improvements in estimated blood loss while adhering to the oncologic principles required for cancer control including obtaining negative margins and performing an adequate extended lymph node dissection [55].

The indications for robot assisted radical cystectomy (RARC) are identical to ORC. There are no absolute contraindications for RARC, although the Pasadena Consensus Panel [56] noted that certain cases should be performed only by experienced surgeons because of their complexity (Fig. 8.2) Although no accepted definition of experienced surgeon exists, the PCP noted that data on surgeon learning curves with RARC suggest that at least 20–30 procedures are needed to flatten the initial learning curve.

Types of challenging cases
Patient with high body mass index
Salvage cystectomy following chemotherapy and radiation treatment
Patient with clinical lymphadenopathy
Patient with clinically advanced disease (ie, T4)
Patient who has had previous prostatectomy, abdominoperineal resection surgery, or low anterior resection surgery
Patient with large bulky tumor
Patient with multiple prior lower abdominal surgeries
Patient with prior pelvic radiation for pelvic malignancy such as prostate or rectal cancer

Fig. 8.2 Challenging cases recommended for experienced robot-assisted radical cystectomy surgeons only [56]

A randomized trial reported that RARC might be associated with lower blood loss as compared to open radical cystectomy (ORC) [57].

Additionally, retrospective investigations demonstrate better perioperative outcomes for RARC patients [58, 59].

Given the high morbidity commonly associated with ORC, potential benefits in terms of perioperative outcomes associated with minimally invasive approaches raised enthusiasm. Nonetheless, the relatively short follow-up of prospective randomized trials, as well as the lack of a control group in retrospective studies evaluating cohorts from high-volume robotic centers, precluded the direct comparison of strong oncologic endpoints between patients treated with RARC and ORC. Moreover, the few retrospective studies directly comparing the two techniques include small cohorts representing the initial experience with the robotic approach. Therefore, the effectiveness of RARC vs. ORC in terms of relevant oncologic outcomes is still a matter of debate [60]. Although no substantial advantages were observed in terms of postoperative complications, RARC in the hands of experienced surgeons results into substantially lower blood loss and lower risk of postoperative transfusions as compared to open surgery [60]. These potential benefits are in part counterbalanced by the prolonged operative time typically associated with RARC [59].

Summarizing the Pasadena Consensus Panel's conclusions: RARC appears to be broadly equivalent to ORC in terms of morbidity and mortality, oncologic outcomes, and complication rates. RARC appears to result in less EBL and a reduced need for transfusion during surgery, and it provides ergonomic value for surgeons, but operative times tend to be longer for RARC than ORC (particularly early in the learning curve or with intracorporeal reconstruction), and, overall, RARC appears to be significantly more expensive than ORC, particularly in low volume centers. Nonetheless, RARC is a viable alternative to ORC if performed by experienced surgeons in high-volume centers. *Surgeon experience and institutional volume strongly predict favorable outcomes for either open or robotic techniques* [56].

Major Concerns of RARC

Seeding of tumour cells (TCC) possible to other organs and peritoneum.

→ Unusual sites of metastatic disease that can be explained with CO₂ pneumoperitoneum pressure have been reported.

No long term results

Lymphadenectomy not always extended

Longer operative time

Higher costs

Despite the emerging role of RARC as a viable alternative to the traditional open approach, criticisms regarding the RARC literature include the lack of long-term survival data and the inherent patient selection bias, in addition to longer operative time and the associated cost [61]. There have also been concerns regarding adherence to key oncologic tenets and the induction of local pelvic, peritoneal and port site recurrences during minimally invasive approaches to RC [62]. The potential seeding of tumor cells as a source of local recurrences is a concern during open and minimally invasive RC [61].

Tumor aggressiveness, occult metastatic disease at surgery, an inhibited host immune response, laparoscopy related factors such as gas insufflation and desufflation, or breaching of oncologic surgical principles, including

vigorous surgical manipulation, specimen morcellation, entry into the bladder and the retrieval method, have been investigated [63–65].

The contribution of CO₂ pneumoperitoneum deployed in minimally invasive surgery remains unknown [61]. Prior animal studies suggested that CO₂ pneumoperitoneum may inhibit the peritoneal immune response against malignant urothelial cells and may contribute to recurrence in the pelvis and at port sites [66]. Prior reports suggested also that high and/or pulsatile pneumoperitoneum, especially in lengthy procedures, may enhance the migration of tumor cells from the venous plexus of the bladder (of which the pedicles are squeezed throughout the procedure) and contribute to early tumor recurrence [63, 67].

During RC tumor spillage may occur in cases of extravesical disease or extensive nodal involvement, or due to technical error, which may risk seeding the peritoneal cavity with UCC [61].

The incidence of EOF (early oncologic failure) decreased with time from 10% in 2006 to 6% in 2015. If these recurrences are surgery related, this trend might be explained by the evolution of the technique of RARC, the learning curve, experience with the procedure and comfort with the robot-assisted platform for surgery [68].

Recently, Hussein AA et al. retrospectively reviewed the IRCC (International Radical Cystectomy Consortium) database of patients who underwent robot assisted radical cystectomy (RARC) since 2003, observing that the incidence of EOF following RARC has decreased with time and that disease related factors rather than technical or laparoscopy related factors have a major role in early oncologic failure after RARC [61].

Radical Cystectomy: Why Is It Still the Best Treatment Option for MIBC?

Best outcomes

Decreased local/regional recurrence of the disease by the eLND

It is indicated also in locally advanced disease pT4 and in the elderly (>80 years)

The use of orthotopic neobladder improves acceptability of RC and patients QoL

Complication rate can be reduced with **mini-invasive surgery**, **“Fast-track surgery”**, **multidisciplinary team** pre- and post-operative (cardiologists, anesthesiologists, physiotherapists, psychologists, geriatricians, urologists), **high volumes hospitals**

Several studies demonstrate that quality surgery with RC and PLND offers excellent locoregional control for patients with clinically localized or locally advanced bladder cancer, even at extended long-term follow-up [69, 70]. Therefore, RC accomplishes a paramount target in bladder cancer. It achieves oncologic control with acceptable morbidity. However, in the modern world, oncologic control is not the only goal when physicians decide to treat cancer patients, as quality of life is very important as well. Even though there can be considerable complication rates, RC remains the preferred choice for most patients with MIBC [71].

To date, Bladder-sparing (BS) therapies NOT convincing...

1. Patients who do not respond to BS will receive RC: this is already an admission that RC is the best treatment

2. Salvage RC is not the same operation than immediate RC: more difficult, with possible higher complication rate and more risky for patients

(this should be discussed with patients before they receive a BS approach)

(Brausi M, Athens 2016)

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9. Minimally Invasive Radical Cystectomy and Its Role and Future in Treatment of Bladder Cancer Patients. Myth or Reality?

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Introduction

Worldwide, about 357,000 new cases of bladder cancer are diagnosed yearly [1]. Bladder cancer is one of the most common types of malignancy worldwide, with almost 20–40% of patients presenting with invasive disease [2]. If not treated, more than 85% will die within 2 years from the diagnosis [3].

Radical cystectomy (RC) and neoadjuvant chemotherapy is the gold standard treatment for organ confined, muscle invasive or recurrent high grade non-muscle invasive bladder cancer. Furthermore, the earlier the cystectomy the better the outcomes [4]. Open radically cystectomy (ORC) with pelvic lymph node dissection (LND) and urinary diversion is the most common modality of treatment for localised muscle invasive bladder cancer and is indicated for patients with aggressive non-muscle invasive cancers such as those with recurrent carcinoma in situ (CIS) [5–9]. RC plus LND has shown to be able to improve survival rates of patients with invasive bladder cancer [10].

Despite the improvement in surgical technique, ORC is still associated with significant early and late complications rates even when performed in referral centres by experienced surgeons. The reported morbidity of ORC is still around 10–68% with a transfusion requirement of around 66%, while the major complication rates range between 10 and 12% and the mortality rates between 1 and 5% [8, 9, 11–14].

With advances in laparoscopy equipment and increasing skills in laparoscopic surgery, numerous centres across the world have incorporated a minimally invasive approach as a viable alternative for selected patients [15–17].

To reduce the incidence of complications rates associated with ORC and to improve overall standard of care, laparoscopic radical cystectomy (LRC) was attempted (Table 9.1) [6, 9, 11, 18].

Nevertheless, compared to laparoscopic prostatectomy or nephrectomy, the spreading of LRC remains limited, mainly due to the technical difficulties associated with the approach [15, 19, 20].

Table 9.1 Literature search of LRC papers reporting >50 cases

Study	Number of patients	Sex M:F	Operative time	Blood loss	Urinary diversion	Conversion	LoHS	Morphine use	Complications
Cathelineau and Jaffe [4]	84	71:13	Median 280 min (215–330)	Median 550 (150–2000)	Ileal Conduit: 33 Neobladder: 51	0	Median 12 days (8–31)	58% required for 1 day	UTI: 1 Haematoma: 3 Fistula: 2 PE: 1 Pyelonephritis: 1 Death: 0 Complication rate: 18%
Castillo et al. [27]	59	46:13	Mean 337 (150–600)	Mean 488 (50–1500)	Ileal Conduit: 30 Neobladder: 25 Indiana Pouch: 4	1	NA	NA	Intraoperative: 7 (vascular injury) UTI: 3 Pneumonia: 1 Wound infection: 1 Ileus: 5 Lymph leak: 2 Fistula: 3 Hernias: 2 Bowel obstruction: 1 Death: 2 Complication rate: 42%
Sighinolfi [56]	83		Mean 520 (264–760)	Mean (376 (200–600)	Ileal Conduit: 43 Neobladder: 26 Ureterocutaneostomy: 14	2	Mean 13.2 (8–19)	NA	Urine leakage: 1 Fistula: 1 Atrium rupture: 1 Death: 1
Huang et al. [40]	85	77:8	Median 320 (210–605)	Median 280 (50–1000)	Neobladder: 85	0	Median 14	NA	Strictures: 4 Fistula: 3 Ileus: 3 Pneumonia: 1 Pyelonephritis: 1 Complication rate: 14.1%
Haber et al. [38]	50	NA	Mean 6.3 ± 0.26	Mean 363 ± 259	NA	NA	Mean 8 ± 3.2	NA	Minor complications 18% Major complications 8%

Study	Number of patients	Sex M:F	Operative time	Blood loss	Urinary diversion	Conversion	LoHS	Morphine use	Complications
Castillo et al. [27]	85	57:19	Mean 279 (180–375)	Mean 436 (50–1500)	Ileal Conduit: 24 Neobladder: 42 Indiana Pouches: 10 Mainz II Pouches: 9	0	Mean 8.8 (4–28)	0	Peri-operative: (5 vascular, 2 evisceration, 2 sepsis) Late: UTI: 3 Stenosis: 1 Reservoir rupture: 2 Mesenteric ischemia: 1 Death: 1 Complication rate: 20%

Study	Number of patients	Sex M:F	Operative time	Blood loss	Urinary diversion	Conversion	LoHS	Morphine use	Complications
Huang et al. [40]	171	151:20	Median 325 (210–605)	Median 270 (50–1000)	Neobladder: 171	0	Mean 13.1 (7–46)	NA	Early (23%): Incisional haematoma: 1 Wound infection: 2 Ileus: 5 DVT: 1 Delirium and agitation: 2 Lymph leak: 11 Pneumonia: 1 Pyelonephritis: 1 Vesico-urethral leak: 7 Pouch-vaginal fistula: 2 Uretero-pouch stricture: 2 Colon-pouch fistula: 1 Ileal anastomotic leak: 1 Ileo-pouch fistula: 2 Mesenteric vein thrombosis: 1 Late (15.2%): Adhesive Ileus: 3 Urine retention: 4 Pouchitis: 5 Pouch stone: 2 Uretero pouch stricture: 9 Vesico-urethral stricture: 3

LoHS length of hospital stay, *DVT* deep vein thrombosis, *NA* not available, *PE* pulmonary embolism, *UTI* urinary tract infection

Despite its ever-growing acceptance, the technique is evolving and continually developing and will only be fully accepted if long term oncological and functional data will show at least comparable outcomes to those of its open counterpart [21, 22]. Furthermore, despite the success numerous centres have reached with LRC, to date, no head to head trial comparing the long-term outcomes and oncological results between the two modalities has been published [13, 19, 23, 24].

Furthermore, its employment across the urological community has been hampered due to issues such as the technical complexity and the steep learning curve [17]. Despite these limitations, this approach has been shown to be safe and effective in experienced hands [15, 25–28]. Robotic surgery has recently gained popularity, threatening to replace select open and laparoscopic procedures. The proposed advantages of robotic surgery over laparoscopic surgery are the increased manoeuvrability, improved vision with ten times magnification, enhanced endo-wrist dexterity, tremor elimination and a shorter learning curve [6, 11, 29, 30].

In this chapter we will review the evidence for laparoscopic cystectomy as well as for robotic cystectomy.

Comparison of Laparoscopic Radical Cystectomy vs. Open Radical Cystectomy

When comparing the two techniques, LRC showed to have longer operative times compared to ORC ($P < 0.00001$; MD: 56.79, 95% CI: 51.07, 62.51) [15, 25]. However, LRC showed significant advantages such as less blood loss, less transfusion requirement, less time to oral intake, less length of postoperative hospital stay, and significantly less analgesic requirement (Blood Loss: $P < 0.00001$; MD: -389.48, 95% CI: -457.06, -321.90; Transfusion rate: $P < 0.00001$; OR: 0.28, 95% CI: 0.17, 0.46; Oral Intake: $P < 0.00001$; MD: -1.35, 95% CI: -1.73, -0.96; Length of Hospital Stay: $P < 0.00001$; MD: -2.45, 95% CI: -3.12, -1.78; Analgesic Requirement: $P = 0.0009$; MD: -24.53, 95% CI: -39.04, -10.01) [15, 25]. No difference was found regarding the lymph node dissection yields between the two groups ($P = 0.58$; MD: 0.49, 95% CI: -1.22, 2.19) [15, 25].

There was no statistical difference between the two groups regarding the occurrence of major complications ($P = 0.70$; OR: 0.86, 95% CI: 0.41, 1.83). However, the ORC group developed significantly more minor complications compared to the LRC group ($P = 0.02$; OR: 0.52, 95% CI: 0.30, 0.89) [15, 25].

There was no difference between LRC and ORC regarding oncological outcomes, except for the nodal positive rate that was significantly higher in the ORC group (Positive Margins: $P = 0.12$; OR: 0.43, 95% CI: 0.15, 1.25; at least pT2N0: $P = 0.31$; OR: 1.23, 95% CI: 0.83, 1.82; pT3-4 N0: $P = 0.61$; OR: 0.90, 95% CI: 0.60, 1.35; Node Positive: $P = 0.02$; OR: 0.51, 95% CI: 0.29, 0.90; Local Recurrence: $P = 0.9$; OR: 1.10, 95% CI: 0.24, 5.02; Distant Metastases: $P = 0.05$; OR: 0.43, 95% CI: 0.31, 1.63) [15, 25].

Comparison of Robotic Cystectomy vs. Open Radical Cystectomy

Although the Robotic radical cystectomy (RRC) procedure is considered in its infancy, several trials reporting the outcomes of RRC have been published.

Comparative studies have shown a lower blood loss rate and significantly lower transfusion rates when RC is performed with the robotic approach (OR -4.51, 95% CI 2.58, 7.89, $p < 0.00001$) [31]. Conversely, operative times are reported to be significantly higher in the RRC cohort (MD, -61.07, 95% CI -83.85, -38.29, $p < 0.00001$) [31]. No significant statistical difference in surgical margins positivity rates between the two groups are reported (OR 0.63, 95% CI 0.38 to 1.05, $p=0.08$) [31].

No significant statistical difference between the RRC or ORC groups in terms of overall complications rates have been found (RD -0.03, 95% CI -0.10 to 1.08, $p=0.30$) [31]. Moreover, there was no statistical difference between the two groups regarding Clavien I-II complications

(RD 0.06, 95% CI -0.01 to 0.13, p=0.10) [31]. Regarding Clavien III-IV, significantly lower complications in the RRC cohort have been reported (RR 1.75, 95% CI 1.14 to 2.68, p=0.01) [31]. Finally, in this comparative study, 10 (2.2%) deaths (Clavien criteria V) in the ORC group were reported compared to 1(0.35%) death in RRC (Clavien criteria V) (RR 0.02, 95% CI 0.00 to 0.05, p=0.04) [31].

Recently, a study comparing the perioperative and oncological outcomes of RRC vs. ORC performed at two high-volume centers has been reported. Although ORC has been associated with shorter operative times, RRC led to lower blood loss and shorter length of stay. No differences were found in terms of high grade complications and positive margins. RRC and ORC provided similar oncologic outcomes.

Finally, a recent meta-analysis of four randomized controlled trials comparing RRC and ORC showed similar results (Table 9.2).

Table 9.2 Patient demographics

Author	No of patients (Lap vs. Open)	Age	M:F	Urinary diversion	Previous surgery	BMI	Follow up	Overall survival rate	Disease specific survival rate	Disease free survival rate
Basillote et al. [34]	13 vs. 11	66.8 ± 9 vs. 58.9 ± 9.2	13:0 vs. 11:0	13n vs. 11n		27.2 ± 2.2 vs. 26.2 ± 2				
Gregori et al. [35]	10 vs. 10	66.6 vs. 65.5	10:0 vs. 10:0	10n vs. 10n		24.2 vs. 23.5				
Guillotreau et al. [36]	38 vs. 30	67.9 ± 9 vs. 64.9 ± 12.3	36:2 vs. 25:5	13i:24n:1u vs. 20i:9n:1u	5 vs. 10	25.9 ± 3.6 vs. 26.1 ± 4.3	30.5 ± 17.2			
Ha et al. [37]	36 vs. 34	67.5 ± 8.9 vs. 55.9 ± 9.8	32:4 vs. 27:7	NS: either n or i	Were excluded	23.2 ± 2.4 vs. 22.7 ± 3.6	22 vs. 67	64.2% (23/36) vs. 72.6% (25/34)	73% vs. 75.3%	70.5% vs. 72.5%
Haber et al. [38]	50 vs. 50	66 vs. 67	38:12 vs. 34:16	32i:18n vs. 37i:13n		27 vs. 26				
Hemal and Kolla [44]	30 vs. 35	58.2 vs. 58.9	28:2 vs. 33:2	30i vs. 53i		24.5 ± 1.9 vs. 25.7 ± 2.6	38 vs. 46	86.67% (26/30) vs. 88.57% (31/35)		76% vs. 80%
Porpiglia et al. [41]	20 vs. 22	63.5 vs. 71	19:1 vs. 20:2	10i:10n vs. 17i:5n			19.5 vs. 19.2		100 (20/20) vs. 95.3 (1/22)	
Wang et al. [42]	14 vs. 24	63.7 ± 10.1 vs. 58 ± 11.3	13:1 vs. 23:1	12i:2n vs. 21i:3n		22.1 ± 3.2 vs. 21.7 ± 2.7				

Comparison of Robotic vs. Laparoscopic Radical Cystectomy

With the appearance of robotic surgery, robotic radical cystectomy has emerged not only as an alternative to ORC but also to LRC. In an observational study, Benito et al. compared LRC to RRC and reported that RRC led to significantly less blood loss, fewer transfusion requirement, and less days to oral intake [32]. Furthermore, they reported that RRC had less intra-operative (1

vs. 3) and post-operative (3 vs. 11) complications than the LRC counterpart. Otherwise, no significant difference was found between the two procedures regarding operative times and length of hospital stay [32].

Discussion

Laparoscopic surgery has advanced considerably in the last decade, extending its use even in difficult prolonged procedures such as radical cystectomies. Since the first LRC was described, numerous centres have published their experience with the procedure [33]. However, only a handful of centres have published data on more than 50 procedures (Table 9.1). Nonetheless, ORC remains the gold standard of treatment for select bladder cancer cases. However, LRC is quickly emerging as a viably safe alternative.

Laparoscopic surgery has rapidly evolved and gained worldwide acceptance as a viable alternative for open procedures. Laparoscopic nephrectomy and prostatectomy procedures have already started replacing their open counterparts; however, LRC is slow to gain such acceptance. The main reason is related to the difficulty of the technique, in addition to the need for urinary diversion, which adds more time to the procedure. Nonetheless, numerous centers have increased their skills with LRC, adding it to their armament of procedures [15, 25, 34–43].

Systematic reviews comparing the two procedures showed that ORC provides shorter operative time than LRC; however, LRC leads to less blood loss, transfusion requirement, shorter length of post-operative hospital stay and less morphine requirement [15, 25, 43]. Furthermore, LRC resulted in more intraoperative complications and more anastomotic stenosis, while ORC had more septic related complications and more patients treated with this approach developed ileus post-operatively [15, 25, 43]. Otherwise, ORC and LRC provided no difference regarding any other peri, intra, or post-operative outcome. More importantly, no difference was found between the two groups regarding survival or disease recurrence [15, 25, 43].

Though numerous studies have reported their centre's comparisons of LRC and ORC [15, 25, 34–38, 41, 43, 44], only two studies concerned more than 50 patients per cohort [38, 40]. Huang et al. compared 63 ORC patients to 108 LRC patients [40]. They found that the ORC group had significantly more blood loss than the LRC group (320 mL vs. 1100 mL; $P < 0.001$). Furthermore, they reported that the LRC group took significantly less time to start oral feeding than the ORC group (2.4 days vs. 4.5 days; $P < 0.001$). There were also significantly less complications in the LRC group (18.5% vs. 30%; $P < 0.05$). Otherwise, they found no difference between the two groups regarding operative time or surgical margins.

While Haber et al. [38], comparing 50 patients in each group, also found significant difference regarding blood loss favouring LRC (363 ± 259 mL vs. 801 ± 684 ; $P = 0.0004$), they also found that the LRC group had significantly longer operative time (6.3 ± 0.26 h vs. 5.3 ± 0.28 ; $P = 0.01$). Otherwise, no other difference was found between the two procedures, especially regarding complications, hospital stay, or surgical margins.

Similarly, variable operative and post-operative findings were echoed by the comparative studies with fewer patient cohorts, [34–36, 41, 42]. Guillotreau et al. reported that the LRC group had significantly less blood loss, postoperative minor complication rate and less opioid requirement [36]. While Wang et al. only found the blood loss was less for the LRC group, otherwise no difference was found [42]. Gregori et al. reported that the LRC group had significantly longer operative time, however had less hospital stay [35]. Porpiglia et al. only found significant difference with the start of oral intake and less analgesic requirement favouring the LRC group [41]. Basillote et al. also reported that the LRC needed less time to start of oral intake and less analgesic requirement, in addition to a shorter hospital length of stay [34]. In a cost

comparison study, Gregori et al. found that LRC led to significantly less total costs than ORC, mainly due to a significantly short length of hospitalisation [35].

Hence thus far, from the reported literature, it is evident that LRC is at least as safe and efficient as ORC, regarding peri and post-operative parameters, with the only parameter favouring ORC which stands out is the operative time [35, 38]. Nonetheless, what are vital to truly determine if LRC can replace ORC are the survival and tumour free rates. The longest oncological follow up period in the literature was reported by Haber et al. on 37 LRC patients. They reported a 5-year overall survival of 63%, a cancer specific survival of 92% and a recurrence free survival of 92% [45]. Though not directly compared to an ORC group, their LRC results suggest comparable survival rates to the open counterpart [45]. To date, all studies comparing LRC to ORC have less than a mean of 3 years of follow up, thus reporting on a relatively short oncological post-operative period. Nonetheless, they reported that no difference was found regarding survival and tumour free rates between the two groups [37, 40, 41, 44].

Though the debate still goes on, laparoscopic skills continue to increase, and the elapse of time will give rise to longer oncological results to determine if LRC is at least equivalent in that regards. Till then, the 5-year survival rate represents the longest reported follow up of patients whom underwent LRC directly compared to an ORC group of patients and have shown that LRC is to par with ORC in this regard. Both groups had similar survival probability estimations with no difference found regarding death rates or disease recurrence.

Comparison between these two groups has suggests that most early surgical outcomes in RRC are better than those achieved with ORC in potentially carefully selected patients [31]. The IRCC, a multi-institutional collaborative society, reported on the largest series of RRC cystectomies of more than 900 patients. They reported a 90-day mortality of 4.2% and overall complication rate of 48% at 90 days of which only 19% were deemed to be high grade [46]. The RRC group was superior to ORC regarding the estimated blood loss and transfusion rates. The ORC cohort had indeed quicker operative times; this is probably a reflection of RRC being a relatively novel technique. It is hoped and expected that with learning curves achieved this difference will be mitigated as well.

With experience and standardisation of the technique, in particular concerning the reconstructive diversion steps, there is potential for further improvement in the early outcomes. Currently both intracorporeal and extracorporeal techniques of UD have been described. The IRCC reported on outcomes between extracorporeal and intracorporeal UD in 935 patient undergoing RCC. The intracorporeal approach led to lower gastrointestinal complications and to lower risk of developing a complication at 90 days when compared to extracorporeal UD [47].

RRC seems to have a relatively short learning curve and to be reproducible. Hayn et al., using operative time, estimated blood loss, lymph node yield and surgical margin rates as surrogate markers of quality reported that it requires 30 cases to achieve reasonable proficiency in RRC [5]. Pruthi et al. studied 50 consecutive patients and found that during the early stages of the learning curve, RRC took longer operative times and was associated with higher blood loss when compared to the cases performed at the end of the learning curve [48]. No differences were reported regarding oncological outcomes. Modular training has been adopted in laparoscopic and robotic prostatectomy with excellent outcomes and could be suggested also in the training for RRC as well [49].

One of the limiting factors in the widespread application of robotic surgery in any urological technique is the perceived high costs of the approach. Obviously, also complications with the need of reoperations and/or readmissions contribute to further expenses. Being RRC potentially a lower morbid procedure compared to ORC, it is hoped that this will compensate for its initial high costs, thus possibly making it cost effective. Lee et al. compared costs between ORC and RRC. They

found that the overall costs (considering also those of complications and their treatment) of RRC are lower than those of ORC, if either Ileal Conduit or cutaneous diversions techniques were used. Conversely, RRC with neo-bladder was more expensive than ORC [7]. With recent evidence suggesting intra-corporeal UD techniques to be lower morbid procedure in comparison to extra-corporeal UD, a further cost-analysis using this technique is warranted.

Based on the current literature, no differences in terms of surgical margin positivity between the two the techniques have been reported. Since RRC is in its adolescent phase only a few centres have reported their long-term oncological results. Raza SJ et al., in a serie of 99 patients who underwent RRC with a minimum follow up of 5 years, recently reported a 5-year recurrence free survival, a cancer specific survival and an overall survival of 52.5, 67.8, and 42.4% respectively [50]. Choudhury et al. found that the disease free and survival rates were comparable between ORC and RRC, with the longest follow up for RRC being 3 years [51–54]. Snow-Lisy et al. have also published their finding on 121 patients who underwent RRC or LRC between December 1999 and September 2008 [55]. They reported similar results to ORC in terms of overall survival, cancer specific survival and recurrence free survival. However, long term oncological results are lacking.

Conclusion

LRC is a safe and efficient modality of treatment that can be added to the urologist's arsenal of treatment options. It is evident that not only is LRC feasible and safe, but also any type of urinary diversion can be successfully performed with this technique. The most important issue remains the oncological outcomes. The 5-years outcomes are equal to those achieved with ORC. Furthermore, LRC was found to be superior in numerous aspects of operative and post-operative parameters to ORC. Only the operative time favoured ORC; however, with increasing skill of the surgeon, the LRC operative time will reduce. While the only issue remaining unresolved is the cost, as discussed taking into consideration every aspect of hospital admission and post-operative care, LRC seems not to be more expensive than ORC.

The steep learning curve could potentially be shortened with RRC. RRC is as safe and effective when compared to the conventional ORC for the management of muscle invasive or high-grade non-muscle invasive bladder cancer. RRC has also shown to result in less blood loss, fewer deaths, and lower high-grade complication rate.

Collaborative trials comparing LRC and RRC techniques to establish which of the two approaches is more effective are needed. Furthermore, more studies are required to investigate the long-term results and to confirm the two procedures as oncological efficient.

With many centres adopting robotic surgery, RRC would most likely be the next logical minimally invasive procedure for muscle invasive bladder cancer rather than LRC. Only time will tell us, as already seen with radical prostatectomy, if the robotic approach will replace the laparoscopic and open surgeries.

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10. Neoadjuvant vs. Adjuvant Chemotherapy: Which Is Right?

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Background

Muscle-invasive urothelial bladder cancer is, in all cases, a potentially life threatening disease. The majority of mortality among patients in whom the disease is apparently confined to the bladder at the time of initial treatment is from distant metastatic failure. T stage is prognostic with regard to risk of death from bladder cancer, with the risk ranging from 63% survival at 5 years for T2 disease to 46% for T3/4 disease (<https://www.cancer.org/cancer/bladder-cancer/detection-diagnosis-staging/survival-rates.html>). Given the high response rates to cisplatin-based chemotherapy in advanced disease, there is a strong rationale for incorporating systemic chemotherapy early in the course of treatment. Thus, the main therapeutic objective of chemotherapy at the time of initial radical treatment is to increase the proportion of patients who are cured of bladder cancer.

Neo-adjuvant Chemotherapy

Neo-adjuvant systemic therapy has an established role in the treatment of several common cancers where it has claimed advantages over adjuvant therapy. At a conceptual level, although the primary aim of systemic therapy in cancer is to control the systemic disease, it may also bring about a clinically important response in the primary tumour. In the case of planned surgery, this may reduce the morbidity of surgery (for example by down-scaling from mastectomy to wide local excision in the case of breast cancer), improve the chance of complete local clearance (for example in esophageal cancer), and enable direct observation of chemo-sensitivity in the individual patient. In the case of planned radiotherapy, down-sizing of the primary may enable more focused irradiation of the tumour with greater sparing of adjacent normal tissues. In addition, where the morbidity of surgery is high, or where the duration of radiotherapy is prolonged, the use of neoadjuvant chemotherapy should permit more rapid treatment of the life-threatening systemic disease where its effects may otherwise be compromised if there is prolonged delay due to surgical recovery times or duration of radiotherapy. Conversely, surgery or radiotherapy is likely to be delayed by the use of neoadjuvant chemotherapy which may result in loss of control of the primary. Furthermore, morbidity associated with neoadjuvant chemotherapy may result in delayed, compromised or even missed radical treatment of the primary. Furthermore, where definitive staging and pathology are based on examination of the final surgical specimen, this is likely to be compromised by the effects of neoadjuvant chemotherapy where possible down-staging may result in inaccurate information to guide further management.

There are two key phase III trials of neoadjuvant chemotherapy in urothelial bladder cancer. The first trial was an intergroup study in the United States. All patients were planned to undergo cystectomy with a diagnosis of T2-4aN0M0 bladder cancer at TURBT. Three hundred and seventeen patients were randomized either to undergo immediate cystectomy or to receive 3 cycles of 4-weekly chemotherapy with methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) prior to cystectomy. The primary endpoint was overall survival. The results demonstrated a 25% reduction in the risk of death equating to a 14% absolute reduction in the risk of dying from any cause within 5 years of

randomization ($p = 0.06$). Although MVAC chemotherapy was associated with predictable toxicity, this did not result in significant compromise in surgery with 18% patients not undergoing planned cystectomy compared with 19% in the immediate cystectomy arm [1]. The International Collaboration of Trialists BA06 30,894 trial included patients with Grade 3 T2, T3 or T4a, N0/x M0 bladder cancer planned for either cystectomy or radical radiotherapy. Nine hundred and seventy-six patients were randomized either to immediate radical treatment or to receive 3 cycles of cisplatin, methotrexate and vinblastine chemotherapy (CMV) prior to undergoing radical treatment. Long term follow-up confirmed 16% reduction in the risk of death ($p = 0.037$) with an absolute reduction of 6% at both 5 and 10 years [2, 3]. Meta-analysis of individual patient data for 3005 patients from these and 9 other trials confirmed a statistically significant survival advantage associated with neo-adjuvant chemotherapy prior to cystectomy. The absolute risk reduction in this meta-analysis was 14%, equating to a 5% reduction in the risk of death at 5 years [4].

There is lack of consensus as to the optimal chemotherapy regimen to be used in the neoadjuvant setting. Neither 4-weekly MVAC nor CMV is widely used now, as other regimens, particularly cisplatin plus gemcitabine, have been shown to be better tolerated with similar efficacy in advanced urothelial cancer [5]. An analysis of 'real world' data suggest that similar pT0 rates are achieved with either MVAC or gemcitabine/cisplatin [6]. Similarly, there is lack of consensus regarding the optimal duration of chemotherapy although patients in the pivotal trials were given three cycles or 12 weeks of chemotherapy. There are no data to support the use of non-cisplatin based regimens in the neoadjuvant setting. Given the likely inferiority of non-cisplatin regimens in the advanced disease setting and the relatively modest benefits of neoadjuvant chemotherapy overall, most patients who are not suitable for cisplatin are likely to proceed directly to radical treatment of the bladder primary without neoadjuvant chemotherapy.

It is undoubtedly the case that neoadjuvant chemotherapy is likely to delay radical treatment in most cases and some have raised concern that delay in local treatment to permit systemic treatment may result in worse cancer outcomes. However, as reported in the neoadjuvant MVAC trial, a similar proportion of patients failed to undergo planned cystectomy in both arms of the trial [1]. Furthermore, in a retrospective analysis of cystectomy patients in Holland, delay in cystectomy of 3 months was not associated

with adverse outcome when adjusted for other factors [7]. Similarly, concerns have been raised that patients who have undergone neoadjuvant chemotherapy are more likely to experience operative complications. In another retrospective, multi-centre series, it seems that operative complications at cystectomy are no more likely in patients who have undergone chemotherapy than in those who have not [8].

The impact of chemotherapy on subsequent pathological staging is undeniable. In the SWOG trial, 30% of patients had pT0 disease at cystectomy following chemotherapy compared with 15% in the control arm [1]. However, at present, for those with a diagnosis of muscle invasive cancer prior to cystectomy, there is no indication for additional treatment after neoadjuvant chemotherapy then cystectomy regardless of pathological findings at cystectomy, and so this loss of information cannot affect patient outcomes. Moreover, as was clearly demonstrated in the MVAC trial and in other case series, complete pathological response at cystectomy is associated with long term survival, whilst, conversely, those with residual disease in the specimen at surgery seemingly gain little benefit from neoadjuvant chemotherapy [9]. It is, therefore, conceivable that patients with residual cancer in the bladder following neoadjuvant chemotherapy may be candidates for treatment intensification in the future. Indeed, the ongoing adjuvant immunotherapy trials will address this question in planned subgroup analyses.

How Can We Select Patients for Neoadjuvant Chemotherapy?

Although the evidence to support the use of neoadjuvant chemotherapy in bladder confined urothelial cancer is very strong, it is clear that many patients still develop metastatic disease and go on to die from bladder cancer while others survive without chemotherapy at all. Conventional staging techniques do not predict which patients will benefit from neoadjuvant chemotherapy, with the relative risk reduction appearing constant across the range of T staging [4]. This does, however, result in a smaller absolute benefit for those patients with lower risk of disease recurrence and this information may be used to enable patients to make an informed decision about the amount of benefit they would be willing to trade for the possible toxicity of treatment. Despite this, for the subgroup of patients with T2 cancer at TURBT in the MVAC trial the median survival was 105 weeks in the cohort receiving chemotherapy compared with just

75 weeks in those who did not, suggesting that even for those with ‘good prognosis’ disease, the benefits of neoadjuvant chemotherapy are clinically meaningful. It should be born in mind that pathological ‘up-staging’ is not uncommon at cystectomy, and so the staging information available at the time of planning neoadjuvant chemotherapy may be unreliable.

At present there are no predictive factors in routine use which can help us select patients who will or will not benefit from neoadjuvant chemotherapy. Such factors could enable us to spare those who will not benefit the toxicity of chemotherapy whilst enabling them to undergo local treatment without delay. Furthermore, it may enable the development of more effective systemic treatments for this subgroup. A recent genomic/transcriptomic classification of bladder cancer has revealed subsets of patients who may gain more benefit than others from neoadjuvant chemotherapy (in as much as they are more likely to experience complete pathological response at cystectomy). It is, therefore, likely that we may be able to make intelligent choices regarding neoadjuvant chemotherapy in the near future [10].

Although the majority of data to support neoadjuvant chemotherapy are from patients undergoing cystectomy, there is increasing enthusiasm for bladder preserving treatment using radiotherapy. The BA06 trial included 403 patients who underwent radical radiotherapy, and the trial was stratified according to radical treatment plan (radiotherapy or surgery or both). The benefits of neoadjuvant CMV chemotherapy appeared not to differ between these subgroups and so it seems rational to offer neoadjuvant chemotherapy to those who plan to undergo radical radiotherapy [3]. More recently it has become clear that the use of concomitant chemotherapy with radiotherapy improves local control. However, it is important not to confuse chemo-radiotherapy, where the objective is to increase radiosensitivity, with neoadjuvant chemotherapy, where the objective is to reduce the risk of systemic failure. Indeed, in the BC2001 chemo-radiotherapy trial, patients were permitted neoadjuvant chemotherapy where indicated, and subgroup analyses suggest that the benefits of chemo-radiotherapy are additional to those gained from neo-adjuvant chemotherapy [11]. Thus patients planning to undergo radiotherapy or chemo-radiotherapy should still be offered neoadjuvant chemotherapy.

Adjuvant

Adjuvant systemic therapy is a mainstay for improving long-term survival outcomes in a variety of common solid tumours, notably breast, lung and colorectal cancer. It has several practical advantages over neoadjuvant therapy: notably it is less dependent on the involvement of multiple specialists at the time of diagnosis (which can be a particular barrier when different specialists are not co-located or do not work in established multi-disciplinary teams). Furthermore, there is no risk that chemotherapy will compromise the ability to safely complete primary surgery due to delay or toxicity. In addition, as the need for chemotherapy may be stratified according to risk, the final pathology and staging results are available to enable decision making prior to embarking on adjuvant therapy. Conversely, as patients need time to recover from primary surgery before embarking on chemotherapy, and as there is some evidence that delay in initiation of adjuvant chemotherapy may result in worse outcomes, it is possible that adjuvant chemotherapy may be less effective than neoadjuvant chemotherapy, particularly when more complex surgery (such as cystectomy) may demand prolonged recovery times before starting chemotherapy.

To date, no properly powered randomized phase III trial has been completed addressing the issue of adjuvant chemotherapy in patients who have had primary local treatment for muscle invasive bladder cancer. The largest and most recent trial, that of the European Organization for Research into the Treatment of Cancer (EORTC) closed early due to slow accrual. The trial originally intended to recruit 680 patients with the primary objective of exploring the impact of adjuvant chemotherapy (using either the MVAC or gemcitabine/cisplatin regimens) on overall survival. However, the trial stopped after recruiting just 284 patients. Nonetheless, this remains the largest single trial and so these data remain informative. Not surprisingly, the trial failed to show a statistically significant impact on overall survival, although there was a trend in favour of this (22% reduction in risk of death from any cause ($p = 0.13$)). There was a significant effect of adjuvant chemotherapy on progression free survival with 48% being alive and progression free 5 years after randomization in the chemotherapy arm vs. 32% in the control arm. Thus, although the trial was incomplete, the

data strongly support the idea that adjuvant chemotherapy improves outcomes [12].

To combat the paucity of adequately powered trials, meta-analyses lend additional weight. Two recent trial-level meta-analyses both confirm a likely survival benefit for adjuvant chemotherapy, with a relative risk reduction of 23% in favour of chemotherapy in both studies [12, 13].

As in the neoadjuvant setting, there is no consensus on the optimal choice of regimen or duration of therapy. In the EORTC trial, investigators chose between four cycles of conventional MVAC, dose-dense MVAC or gemcitabine cisplatin and this is a reasonable basis for guidance. There are no direct data to support the use of non-cisplatin containing regimens in the adjuvant setting, and such regimens should generally be avoided in patients who are fit enough to receive cisplatin. At present, there is insufficient information on which to base a decision regarding adjuvant chemotherapy in patients who are not suitable for cisplatin.

Can We Select Patients Who Benefit from Adjuvant Chemotherapy?

Patients who have primary cystectomy will have final pathology and staging available to guide the planning and choice of adjuvant chemotherapy. It is, thus, possible to consider absolute risk (and, consequently, absolute risk reduction associated with chemotherapy) with greater accuracy than can be applied in the neoadjuvant setting. There were few patients with T2 disease included in the EORTC study, but subgroup analysis did not suggest that T stage was associated with a differential effect of adjuvant chemotherapy. Furthermore, an individual patient level meta-analysis found no evidence that chemotherapy was more or less effective in patients according to T stage [14].

At present there are no predictive markers which have been evaluated in the adjuvant setting, although it seems likely that predictive markers ‘learned’ in the neo-adjuvant setting may also predict benefit from the same drugs used in the adjuvant setting.

How Can We Choose Between Neo-adjuvant and Adjuvant Chemotherapy?

There are no trials comparing the two approaches. Indirect comparison between the sets of data described above, would suggest that the relative and absolute risk reductions associated with neo-adjuvant and adjuvant treatment are similar. However, the quality of the data in favour of neoadjuvant chemotherapy would support a stronger recommendation than could be given for adjuvant therapy, and this is reflected in many of the guidelines. There are some patients who, of necessity, can only be considered for adjuvant therapy: in particular, patients who have impaired renal function prior to radical treatment may not be suitable for cisplatin at that time but may become so after successful surgery. Similarly, some patients are 'upstaged' from high risk non-muscle invasive (NMI) disease to muscle invasive disease at cystectomy. There being no case to use neoadjuvant chemotherapy in NMI disease, chemotherapy could be considered in the adjuvant setting for these patients. Some patients have a significant burden of acute, local symptoms at diagnosis and, although neoadjuvant chemotherapy may help ease these symptoms in some cases, in others, immediate radical treatment (either surgery or radiotherapy) may be preferable.

Variants

Upper tract urothelial cancers are associated with a poor prognosis. To date, there are no randomized data to support the use of peri-operative chemotherapy in this relatively rare condition. Accurate pre-operative pathological staging is often not available in such cases (due to the technical challenges in accessing and biopsying the upper tracts endoscopically), and so pre-operative consideration of neoadjuvant chemotherapy is rarely feasible. However, as nephro-ureterectomy is generally a less morbid procedure than cystectomy, the option to deliver timely adjuvant chemotherapy is likely to be there for patients with invasive disease. The United Kingdom National Cancer Research Institute is conducting a randomized phase III trial of four cycles of 3-weekly cisplatin plus gemcitabine compared to best supportive care (POUT trial) [15].

The majority of patients in the pivotal trials had typical urothelial cancers (with transitional cell morphology). At present, the value of peri-operative chemotherapy in other types, such as pure squamous carcinoma, neuroendocrine, small cell or adenocarcinoma are sparse. Retrospective

case series in small cell bladder cancer patients suggest that best outcomes are associated with combined modality treatments which include chemotherapy, although there are no data to guide a choice between adjuvant and neoadjuvant administration [16, 17].

Lymph Node Positive Disease

Lymph node involvement at diagnosis is associated with very poor outcomes and such patients were largely excluded from the trials discussed above. In the individual patient meta-analysis of the neoadjuvant clinical trials there were a small proportion of studies which included patients with lymph node positive disease. The authors comment only that the reduction in risk of death is not affected by the presence or absence of lymph nodes at trial entry, suggesting that node positive patients may also benefit from neoadjuvant chemotherapy [4]. Similarly, in the individual patient meta-analysis of adjuvant chemotherapy nodal status did not predict for a differential effect of chemotherapy [14]. However, in the EORTC adjuvant trial there was an interaction for positive nodal status at cystectomy and the effect of chemotherapy on survival (but not progression free survival), suggesting that the conclusions with regard to overall survival gain may not hold true for patients with node positive disease. Therefore, there remains considerable uncertainty regarding the benefits of either neoadjuvant or adjuvant chemotherapy in patients with node positive disease.

Guidelines

The UK National Institute for Health and Care Excellence (NICE) have recommended that patients with muscle invasive bladder cancer should be offered neo-adjuvant chemotherapy prior to either cystectomy or radiotherapy. They have also recommended that adjuvant chemotherapy should be considered only for patients in whom neoadjuvant chemotherapy was not previously indicated due to upstaging from NMI disease at the time of cystectomy (<https://www.nice.org.uk/guidance/ng2>). The European Association of Urologists (EAU) similarly recommend neoadjuvant chemotherapy with cisplatin-based combination chemotherapy for all patients with T2—4a N0 M0 bladder cancer. They also recommend that adjuvant chemotherapy be offered to those with T3/4 N0 M0 or Tany

N1 M0 bladder cancer who have not received neoadjuvant chemotherapy. The US National Comprehensive Cancer Network (NCCN) permits neoadjuvant chemotherapy for patients with muscle invasive bladder cancer, but restrict their advice on adjuvant chemotherapy to patients with T3/4 or N+ disease. They do not recommend standard MVAC but favour dose dense MVAC or gemcitabine/cisplatin (using either the 3 or 4-weekly schedules) (https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#bladder). The European Society for Medical Oncology (ESMO) recommend neoadjuvant chemotherapy commenting that there is insufficient evidence to favour adjuvant chemotherapy [17].

New Developments

The advent of immunotherapy using immune checkpoint inhibitors as an effective therapy for advanced urothelial cancer raises the possibility that this new modality could be incorporated into existing multimodality treatment for muscle invasive bladder cancer. At present, trials are underway exploring neoadjuvant immunotherapy (alone and in combination with chemotherapy) as well as adjuvant immunotherapy (permitting prior neo-adjuvant chemotherapy) in patients who plan to have or have had cystectomy for muscle invasive bladder cancer.

Summary

There is high level evidence to support the use of neoadjuvant cisplatin-based combination chemotherapy in patients with muscle-invasive, organ confined, urothelial bladder cancer. Where this is not practical, data from meta-analysis support the use of adjuvant chemotherapy, although there is no level one evidence to support this practice. This evidence is reflected in national and international guidelines. Despite these data, the absolute benefits of systemic therapy are modest, and careful patient selection may be necessary to obtain optimum results. At present, there are no established predictive markers to aid in choosing which patients should and should not receive chemotherapy. There are several areas of uncertainty, in particular with reference to the value of either treatment in patients with nodal disease or in those with atypical pathology.

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11. Radiotherapy for the Treatment of Muscle-Invasive Bladder Cancer

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Introduction

Muscle invasive-bladder cancer (MIBC) accounts the 20–25% of all bladder cancers [1]. There are two curative options for non-metastatic MIBC: radical cystectomy (RC) with or without chemotherapy and trimodality (TMT) approach (re-transurethral resection of the bladder tumor i.e. re-TURBT followed by concomitant chemo-radiotherapy) [2, 3]. In T2-T4 N0 M0 MIBC, RC with or without chemotherapy achieves a survival rate of 50–60% at 5 years [2]. However, RC may adversely affect many aspects of quality of life (QoL) mainly in the urinary function and sexual domains [4].

Bladder cancer patients will continue to present at advanced age, and some of them refuse or are not the ideal candidates for RC due to high risk of perioperative mortality (as a consequence of concomitant tobacco-related comorbidity). Bladder preservation based on TMT is an option for MIBC patients unwilling to undergo RC or unfit for radical surgery. In the second case, TMT may not always be feasible and bimodal approach like re-TURBT followed by radiotherapy (RT) may be considered. In patients with locally advanced or metastatic MIBC short palliative RT may offer good palliation with hemostatic and/or antalgic effect.

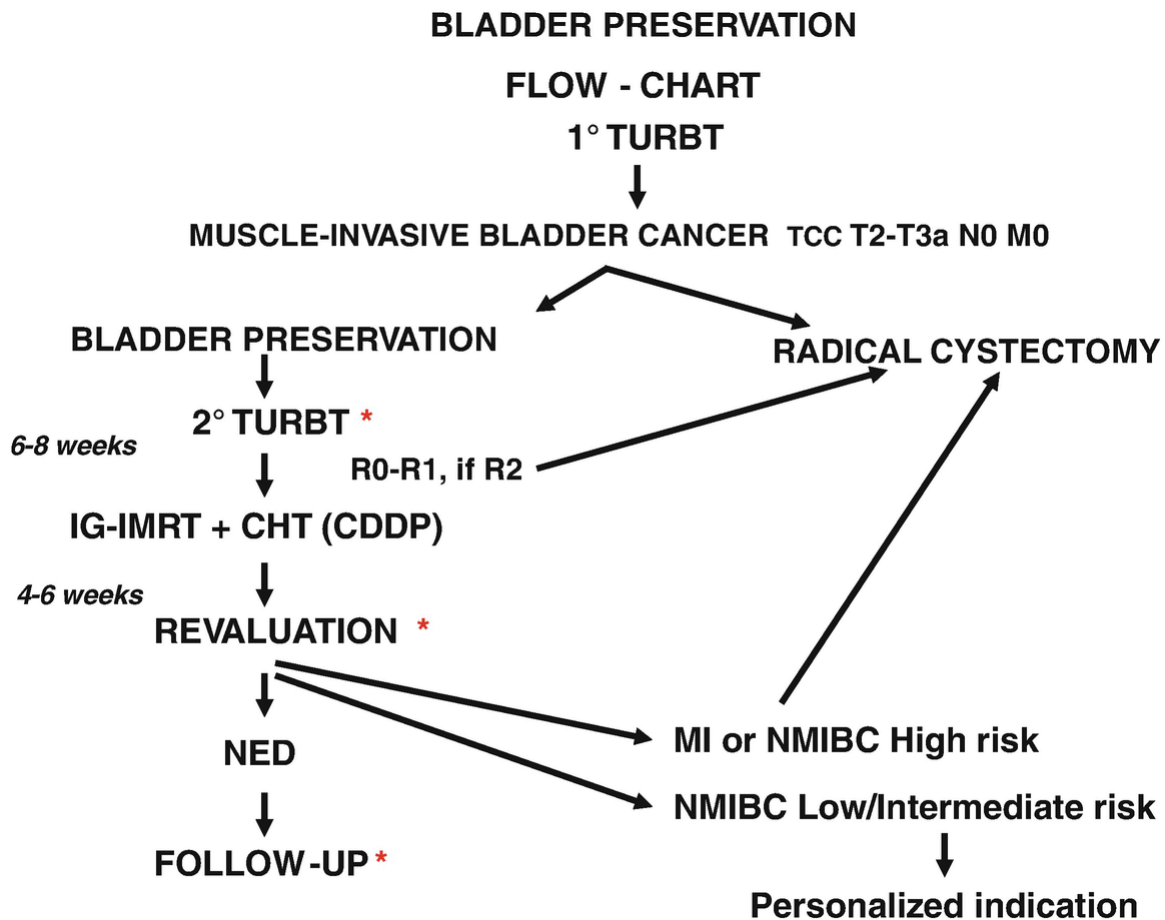
There is a general underutilization of TMT-based bladder preservation in fit-for-RC MIBC patients, however, recent numerous studies showing similar Overall Survival (OS) of two approaches (TMT and RC) should facilitate counseling patients with this particular condition.

Combined Modality Treatment: What? Who? When?

Based on several data partial cystectomy, radical transurethral resection, chemotherapy, and RT when used alone cannot achieve adequate local control in MIBC [5, 6]. Similarly, bimodal approaches including TURBT followed by radio- or chemotherapy alone seem suboptimal and should be reserved only for very selected cases. Although randomized studies are missing, numerous prospective series and phase II studies showed that the combination of all three modalities (surgery, chemo and RT) called TMT offers the best oncological outcomes, comparable to RC with or without chemotherapy, with salvage cystectomy being reserved for patients with incomplete response or local muscle-invasive relapse [7].

TMT includes the combination of maximal tumor de-bulking followed by concomitant chemo-radiotherapy. Maximal visible resection of bladder tumor (re-TURBT) is required, otherwise the presence of macroscopic residual tumor drives mandatory to RC. Patients should undergo re-TURB 4–6 weeks after initial resection to remove any residual disease. For what concerns chemo-radiotherapy there are two protocols: the first includes a dose of 45–45 Gy/4–5 weeks of radiation with or without induction chemotherapy followed by a cystoscopy and re-biopsy of any residual tumor, if the biopsy is negative a consolidation chemo-radiotherapy is provided (so called “split course” employed mainly when more advanced

cases are treated, in order to exclude early progression). Incomplete responders proceed with RC [8]. The second one consists in continuous chemo-radiation to a total dose of 55–66 Gy/5–6 weeks, a cystoscopy and re-biopsy are performed after the treatment [9, 10]. An example of the TMT treatment algorithm (Fig. 11.1) is provided by the Italian Group Rete Oncologica Lombarda (ROL) [10].



* According to minimum standard of ROL protocol

Fig. 11.1 TMT treatment algorithm by ROL (Rete Oncologica Lombarda, Italy) [10]. *TCC* transitional cell carcinoma, *TURBT* transurethral resection of the bladder tumor, *IG-IMRT* image guided-intensity modulated radiation therapy, *R* residual (tumor), *CHT* chemotherapy, *CDDP* cisplatin, *MIBC* muscle invasive bladder cancer, *NMIBC* non muscle invasive bladder cancer, *NED* no evidence of disease

Chemotherapy is an integral part of TMT [6], due to its radiosensitizing effect and reduction of distant metastases, however, there is no consensus on the best chemotherapy scheduling. Current regimens include: cisplatin as single agent is the most common employed (with a weekly or every three

weeks schedule), in patient unfit for it low dose gemcitabine or carboplatin may be an alternative. A combination of fluoruracil and mitomycin C could also be adopted [11].

The published reports on the TMT include usually two cohorts: (1) patients with severe medical comorbidities (high-risk surgery) or with unresectable disease and (2) patients with limited disease who wish to avoid radical surgery [12]. The latter, with the most favorable prognosis, constitutes the ideal patient population for bladder preservation. The optimal criteria for TMT are (1) T2-T3a N0; M0 (2) no significant baseline urinary dysfunction; (3) able to undergo maximal TURBT followed by concomitant chemo-radiotherapy; (4) completeness of resection in re-TURBT; (5) solitary lesion (multiple lesions or concomitant extensive carcinoma in situ are usually excluded); (6) absence of hydronephrosis; (7) fit and well counseled about the possibility of a salvage RC in case of recurrence and (8) able to undertake a strict post treatment surveillance with cystoscopy and radiologic follow-up. The presence of variant histology out of urothelial does not exclude a TMT program [13].

It has been estimated that about 10–15% of patients fit-for-RC meet the criteria for TMT [12]. Therefore careful selection of patients is of enormous importance to offer safe organ preservation to an otherwise operable cohort [14]. Obviously, multidisciplinary effort including experienced urologists, medical oncologists, and radiation oncologists and comprehensive patient involvement is required [15].

Radiotherapy Techniques (Regimen and Doses)

A different range of dose of irradiation, fractionation schedules, sequences of treatment and volumes delineation have been applied. The standard fractionation usually is of 1.8–2 Gy/fraction with the total irradiation dose to the whole bladder being approximately 55–66 Gy, to the tumor bed up to 70 Gy and 45–50 Gy to the pelvic lymph nodes. Several studies demonstrated that a total dose >55–60 Gy was associated with increasing local control suggesting the importance of dose escalation on the outcome for bladder cancer [16, 17].

The radiation treatment volume should include the whole bladder and the pelvic lymph nodes. Support for nodal irradiation comes from surgical studies demonstrating that the extent of lymph node dissection improves

survival rates, even in node-negative patients [18, 19], related probably to the high rate of occult pelvic micro-metastases [20]. However, Tunio et al. found no difference in bladder preservation, disease-free survival, and OS rates between patients randomized to receive whole-pelvis (n = 120) or bladder-only RT (n = 110) [21]. An even more restrictive volume was irradiated within the bladder cancer 2001 trial (BC 2001). Patients were randomly assigned (1:1 ratio) to undergo RT with or without synchronous chemotherapy with fluorouracil and mitomycin C and either whole-bladder RT or modified volume irradiation (in which not all the bladder received a full dose of radiation). Remarkably, pelvic lymph node relapse was documented only in 9 patients (4.9%) in the chemo-radiotherapy group and 12 (6.7%) in RT group [6].

The other controversy concerns the maximum RT dose to the whole bladder or using a boost of the tumor bed in order to reduce the long term urinary toxicity. Based on the published literature there was no differences in toxicity or tumor control treating with a full dose to the bladder alone vs. 80% of the dose to the bladder with full dose to the tumor bed. For this reason the most common approach is to treat the residual bed to the high dose of radiation (66 Gy) with a dose to the whole bladder of approximately 54 Gy [22, 23].

The recent advances in the RT field, such as the introduction of intensity modulated radiotherapy (IMRT), have improved conformity of the radiation dose to the target volume and reduced the gastrointestinal and genitourinary toxicity [24]. In a dosimetric study, van Rooijen et al. [25] demonstrated a significant small intestine and rectum dose reduction when using IMRT, maintaining adequate target coverage. Similarly, Hsieh et al.'s study on 19 MIBC patients, showed a superior sparing capability of IMRT without a detrimental effect on local tumor control [26].

The implementation of image guided radiotherapy (IGRT) further improved normal tissue sparing by a reduction in so called “safety margins” required for RT set-up uncertainty. IGRT-based dose escalation using Lipiodol fiducial markers (visualization of boost area) may further improve tumor control [27].

Recently the GEC-ESTRO (Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology) published the guidelines on brachytherapy associated with external beam radiotherapy (EBRT) for a bladder preservation in MIBC [28].

Controversies and Evidenced Based Approach Supporting TMT

TMT, based on re-TURBT followed by concomitant chemo-radiotherapy has been largely demonstrated as the most effective bladder preservation strategy [29]. This approach can be considered a competing alternative to RC in MIBC.

Indeed several retrospective and prospective non-randomized studies were performed to compare the efficacy of RC with EBRT. What emerges when evaluating these studies is the bias in patient selection: usually patients undergoing cystectomy were more likely to have earlier stage and smaller tumors, better performance status, and younger age than patients undergoing irradiation [30]. Tumor staging, which is pathological in RC and clinical in TMT, resulted to be another confounding factor making inappropriate comparison between the two treatment strategies by non-randomized studies. In-fact stage discrepancy can occur in up to 50% of patients [31] due to well-known under-evaluation of clinical staging compared to the surgical one.

Moreover, advanced age, worse performance status and comorbidities, that are more frequent in patients receiving TMT than RC, are important variables that can further confound the comparison of the two treatment approaches.

Presently, despite the presence of confounding variables (mostly against TMT), the comparison of 5-year OS rates reported in the TMT and RC series suggests that TMT might be associated with even better outcome in patients with MIBC [7]. Furthermore, after TMT, approximately 75% of surviving patients maintain an intact and functional urinary bladder and approximately 21% of patients undergo salvage cystectomy for a local infiltrating failure [32, 33].

Multiple prospective Radiation Therapy Oncology Group (RTOG) protocols have evaluated bladder preserving combined-modality therapy (CMT) for MIBC, reserving cystectomy for salvage treatment. Four hundred sixty-eight MIBC patients were enrolled onto six RTOG bladder-preservation studies, including five phase II studies (RTOG 8802, 9506, 9706, 9906, and 0233) and one phase III study (RTOG 8903).

In a RTOG pooled analysis of long-term outcome of selective bladder-preserving CMT in the multi-institutional setting, this treatment approach resulted in low rates of invasive tumor recurrence (10-year invasive Local Failure 14%) and high long-term Disease Specific Survival (DSS) at 5- and 10-year of 71% and 65%, respectively and OS at 5- and 10-year of 57% and 36%, respectively, with 80% of patients retaining an intact bladder at 5 years [34].

Recently, long-term bladder preservation treatment outcomes published from a large single-center cohort of patients with cT2-4a MIBC treated at the Massachusetts General Hospital demonstrated 5-year and 10-year OS rates of 57% and 39%, respectively, and 5-year and 10-year DSS rates of 66% and 59%, respectively. These retrospective and observational cohorts highlight that TMT and RC may result in similar oncologic outcomes in appropriately selected patients [35].

To date only small, non-adjusted case control series of TMT vs. RC has been reported and demonstrated no differences between the groups [36]. A study published in 2017 used a propensity score matched cohort analysis to compare oncological outcomes between patients treated with RC or TMT. A total of 112 patients were included after matched (56 who underwent RC and 56 treated with TMT). The 5 year DSS rate was 73.2% and 76.6% in the RC and TMT groups, respectively ($p = 0.49$). Salvage cystectomy was performed in 6 (10.7%) of 56 patients who received TMT [37]. The same method has been applied in another study, where 50 patients treated with RC were compared with 29 treated with TMT using the propensity score matching. The distant metastases free survival (58% vs. 67%), the OS (56% vs. 57%) and cancer specific survival (69% vs. 63%) rates were similar between the RC and TMT groups. One exception was the 5-year local recurrence free survival resulting significantly better in the RC group (74% vs. 35%) [38].

The only study showing somehow inferior results with bladder preservation is a large retrospective analysis of the National Cancer Data Base including 1257 (9.8%) and 11,586 (90.2%) patients who received TMT and RC, respectively. Inverse probability of treatment weighting (IPTW)-adjusted Kaplan-Meier analysis showed that median OS was similar between the TMT (40 months, 95% confidence interval [CI] 34–46) and RC groups (43 months 95% CI 41–45; $p = 0.3$). In IPTW-adjusted Cox regression analysis with a time-varying covariate, TMT was associated with

a significant adverse impact on long-term OS (hazard ratio 1.37, 95% CI 1.16–1.59; $p < 0.001$). No difference with between RC and TMT was observed in older individuals [39]. Definitely, retrospective nature and patient selection issues can at least partially explain the contradictory findings of this series.

As mentioned above bladder cancer is considered a disease of the elderly, and current data show that 23–35% of patients aged between 70 and 80 years do not receive any curative therapy and this rate increases to 35–55% for those aged over 80 [40]. Weizer et al. reviewing the RC outcomes in elderly MIBC patients estimated the 30- and 90-day peri-operative mortality range were 0–9.5% and 0–11%, respectively [41]. A review of 12 retrospective studies including 496 elderly patients treated with TMT with curative intent showed its feasibility and satisfactory toxicity profile with tumor outcomes equivalent to RC. In details the median 5-year Cancer specific survival (CSS) was 52%, comparable to the 5-year CSS of 28–68% reported in the elderly surgical review by Weizer et al. [42].

Ideally, a phase III trial randomizing MIBC patients to RC vs. TMT would allow to compare these two strategies. Regrettably, the United Kingdom Selective Bladder Preservation Against Radical Excision (SPARE) trial has been prematurely closed due to poor accrual and frequent non-compliance with assigned arm (24% patients randomized to RC received RT, underling the issue of patient preferences) [43].

Conclusion Organ-preservation approaches with multimodality treatments have become standard for numerous malignancies (for example, breast, anal and head and neck cancers). Numerous non-randomized studies showed that TMT may offer similar tumor outcome compared to RC with the benefit of intact bladder in a great majority of patients. Therefore, this option should be discussed in highly selected patients motivated to preserve their urinary bladder.

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12. Immunotherapy and New Combinations in Muscle-Invasive Bladder Cancer

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Introduction

Cancer cells are characterized by the progressive accumulation of genetic aberrations and the loss of normal self-regulatory processes [1]. As a consequence they express specific antigens that prompt the presentation of peptides bound to major histocompatibility class I (MHCI) molecules on their surface differentiating them from their normal counterparts. This would makes cancer cells recognizable by the immune system and therefore a valid target for CD8+ T Lymphocytes creating the concept of cancer immunosurveillance [2, 3].

Nonetheless, removal of cancer cells by CD8⁺ T Lymphocytes is just one stage of a much more complex interaction denominated *Cancer-Immunity Cycle* that controls the equilibrium between the recognition of nonself and the prevention of autoimmunity.

The uncover by Allison et al. in the early 1990s of a T cell inhibitory pathway known as the cytotoxic T Lymphocyte Antigen-4 (CTLA-4)-B7 paved the road for further discoveries in the field like the identification of the program death-1 protein (PD-1) and its ligands (PD-L1/L2) [4]. The identification of these physiological “brakes” to the immune response that have the function of avoiding self-immunity, has led to the development of a novel class of cancer immunotherapy so called “check-point inhibitors” that specifically blocks immune effector inhibition (“release the brakes”), strengthening and potentially intensifying preexisting anticancer immune responses.

Cancers with a high rate of somatic mutations exhibit more tumor-specific antigens and therefore should prompt an easier recognition and anti-tumor response by the immune system [5, 6]. Muscle invasive bladder cancer (MIBC) is known to encompass a high number of somatic mutations and therefore is presumed to be a highly immunogenic tumor and therefore an exceptional candidate for treatment with strategies directed to invigorate the immune response. Moreover, already four decades ago, Morales et al. demonstrated the value of stimulating the immune system of patients as a treatment strategy to prevent recurrence or progression of non-muscle invasive bladder tumors through the intravesical instillation of Bacillus Calmette–Guerin (BCG) [7].

This chapter will review the current available evidence of immunotherapy as a treatment strategy for MIBC in the different settings and will also discuss future directions including the role of combinations of different strategies.

Immunotherapy in MIBC: Clinical Evidence

The first signals of activity of immunotherapy in MIBC originated in the metastatic setting. A number of phase I studies were conducted including multiple tumour types and out of these trials, signs of remarkable efficacy in bladder cancer were noticed with response rates and survivals unprecedented in heavily pre-treated patients [8]. These results prompted an

intense clinical development in further stages leading to phase II and phase III studies specifically designed to metastatic urothelial cancer (mUC). The phase II trials conducted that comprised a larger number of patients refined the benefit firstly observed in early stages but showed consistency across different compounds in terms of activity and safety. The recently completed phase III studies have come to confirm that immunotherapy is an effective and overall well-tolerated strategy in mUC and should be considered as another option for these patients. Nonetheless, responses seem to be limited to about 20–25% of the patients in mUC and no valid predictive biomarker has been identified yet, leading to an intense research in this field.

Beyond the development of immunotherapy in advanced stages, clinical research and multiple resources are currently devoted to earlier settings such as the neo-adjuvant and adjuvant contexts.

The Neoadjuvant Setting

The value of the neoadjuvant treatment for MIBC has been demonstrated for more than 15 years. An individual participant data meta-analysis on 11 randomized trials demonstrated an absolute benefit in the 5-year overall survival (OS) rate of 5% (from 45 to 50%) [9]. A platinum-based combination chemotherapy is the standard of neoadjuvant treatment for MIBC [10].

Regarding immunotherapy, a number of approaches are being tested in this setting. The chimeric adenovirus *enadenotucirev* was tested in a phase I study where this virus was given preoperatively both intratumor and intravenously. Virus delivery induced high local CD8+ cell infiltration in the majority of examined tumor samples and was well tolerated, with no treatment-associated serious adverse events [11]. There are ongoing studies with this compound including the combination with the checkpoint inhibitor nivolumab [SPICE study; NCT02636036]. Other combos are being tested and a phase I trial will evaluate the peri-operative addition of AGS-003-BLD, an autologous dendritic cell-based immunotherapy, to standard cisplatin-based chemotherapy [NCT02944357]. Additionally a phase I trial evaluated the toxicity of intravesical recombinant Fowl pox -GM-CSF and/or -TRICOM, but it was not followed by a formal evaluation of its clinical efficacy [12]. The “N-ABLE” study assessing the value of peri-operative CDX-1307, targeting bHCG and the mannose receptor, closed for

poor accrual [NCT01094496]. A study about the addition of an oncolytic virus, Reolysin[®], to standard neoadjuvant chemotherapy was withdrawn by the company “reprioritizing clinical plans to focus on later-stage studies” [NCT02723838].

Another area of intense development in the neoadjuvant setting includes the checkpoint inhibitors. This therapeutic class seems a promising option in this setting with especial interest in the cisplatin-ineligible MIBC patients who represent almost half of the overall bladder cancer population [13]. A number of initiatives are recruiting patients intensively and are summarized in Table 12.1. Special attention merits the ABACUS study [NCT02662309] that is a multinational European Academic initiative that test in the preoperative setting the value of the administration of two three-weekly cycles of atezolizumab followed by cystectomy. Accrual is expected to be completed by Q2 2018.

Table 12.1 Ongoing clinical trials based on neoadjuvant administration of checkpoint inhibitors in MIBC patients

Trial ID	Phase	Interventional arm	Control	Primary endpoint	Country
<i>Cisplatin-eligible patients</i>					
NCT02690558	2	Pembrolizumab + gemcitabine + cisplatin (4 cycles)	None	Pathological down-staging to <pT2pN0	US
NCT02736266	2	Pembrolizumab (3 cycles)	None	Pathologic complete response	Italy
NCT03294304	2	Nivolumab + cisplatin + gemcitabine (4 cycles)	None	Pathologic down-staging to ≤pT1pN0	US
NCT02365766	1b	Pembrolizumab + cisplatin + gemcitabine (4 cycles)	None	Adverse events	US
	2	Pembrolizumab + cisplatin + gemcitabine (4 cycles)	None	Pathologic muscle invasive rate (ypT0, Tis, Ta, T1 ypN0)	
<i>Cisplatin-ineligible patients</i>					
NCT02845323	2	Nivolumab + urelumab (2 cycles)	Nivolumab (2 cycles)	Tumor infiltrating CD8+ T cell density at cystectomy	US

Trial ID	Phase	Interventional arm	Control	Primary endpoint	Country
NCT02365766	2	Pembrolizumab + gemcitabine (4 cycles)	None	Pathologic muscle invasive rate (ypT0, Tis, Ta, T1 ypN0)	US
NCT02812420	1	Durvalumab + tremelimumab (2 cycles)	None	Extreme toxicity (grade 3/4 AE, delay of surgery ≥2 months due to AE)	US
NCT03234153	2	Durvalumab + tremelimumab (4 cycles)	None	Objective response rate	Switzerland
NCT03212651 (PANDORE)	2	Pembrolizumab (unknown number of cycles)	None	Pathologic complete response rate	France
NCT02451423	2	Atezolizumab (MPDL3280A) unknown number of neoadjuvant cycles, 16 adjuvant cycles	None	?	US
NCT02662309 (ABACUS)	2	Atezolizumab (2 cycles)	None	Pathologic complete response rate	UK

The Adjuvant Setting

Despite the previously referred evidence about the value of neoadjuvant therapy and the recommendations of the most relevant international guidelines, the use of neoadjuvant chemotherapy still remains clearly insufficient in the real world (less than 16%). This is probably due to the never confirmed-belief that chemotherapy decreases the access of patients to surgical procedures due to complications during the chemotherapy administration [14, 15]. In resected patients who were not treated with neoadjuvant chemotherapy, adjuvant chemotherapy is associated with a 23%-decrease in the 5-year OS rate and is a valid option [16].

Immunotherapy is also trying to define its role in this setting. Table 12.2 displays the ongoing trials on adjuvant immune therapies, mostly being checkpoint inhibitors. The NCT01353222 trial assessing a HER2-targeted therapy, DN24-02, ended early due to “administrative reasons”.

Table 12.2 Ongoing clinical trials based on adjuvant immunotherapy in MIBC patients

Trial ID	Phase	Interventional arm	Control	Primary endpoint	Country
<i>After chemo-radiation</i>					
NCT03171025 (NEXT)	2	Nivolumab (12 cycles)	None	2-year failure-free survival	US
<i>After surgery</i>					
NCT03244384 “AMBASSADOR”	3	Pembrolizumab (18 cycles)	None	5-year DFS, 5-year OS	US
NCT01435356 (MAGNOLIA)	2	ecMAGE-A3 + AS15 ASCI (13 injections)	Placebo	5-year DFS	US ^a
NCT02450331 (IMvigor010)	3	Atezolizumab (16 cycles)	None	DFS	Switzerland? ^b
<i>Concomitant with radiotherapy, then maintenance</i>					
NCT02891161 (DUART)	1b	Durvalumab (12 months after radiotherapy)	None	DLT, 1-year PFS, DCR	US

DCR disease control rate, *DFS* disease-free survival, *DLT* dose limiting toxicities, *OS* overall survival, *PFS* progression-free survival

^aIn patients with MAGE-A3 positive muscle invasive bladder cancer after cystectomy

^bIn patients ineligible for cisplatin-based therapy

The First Line

Unfit Patients

For decades, there has not been a universally accepted regime for patients with mUC and *unfit* to receive a platinum-based chemotherapy regimen. The combination of carboplatin-gemcitabine has probably been the most commonly utilized based on the results of the EORTC study 30,986 communicated by De Santis et al. [17].

Recent data from immunotherapy trials in this context has increased the standard options and has open new opportunities. Thus, two phase II trials testing respectively a PD-1 inhibitor such as pembrolizumab and a PD-L1 inhibitor like atezolizumab, have shown remarkable activity and favorable safety profile in this patient population gaining recent approval by the regulatory authorities. Pembrolizumab was initially developed in a phase I

basket trial [9] and the preliminary positive results prompted the launch of a multicentre, single-arm, phase 2 study (KEYNOTE-052) where 374 cisplatin-ineligible patients with mUC not previously treated with systemic chemotherapy received pembrolizumab 200 mg every 3 weeks. Eighty-nine patients (24%) had an objective response of which 74 (83%) were ongoing at the time of the study analysis. The most frequent grade 3/4 toxicities were colitis (5%), muscle weakness (5%), fatigue (2%), and alkaline phosphatase increase (1%). One patient died because of side effects related to the immunotherapy. Mature OS data is expected soon [10]. Atezolizumab was tested in mUC unfit patients as part of the phase II study IMvigor 210. One hundred and nineteen patients received three-weekly atezolizumab at 1200 mg. The response rate was 23% (lower than historical data) but including 9% of complete responses and a long duration of response (median duration not reached and 70% of responses ongoing). The median OS was 15.9 months, which is about 7 months longer than the data from the EORTC study 30,986. Safety was overall good, with fatigue, diarrhea and pruritus as the most frequent treatment related adverse events occurring in 30%, 12% and 11% of the patients, respectively. One patient died due to sepsis that was considered treatment-related [18].

The FDA and EMA have recently approved both pembrolizumab and atezolizumab for untreated patients with mUC and that are not eligible for cisplatin-based chemotherapy.

Fit Patients

The standard of treatment for mUC patients who are well enough to receive cisplatin-based chemotherapy [*fit*] remains platinum-based combinations such as gemcitabine-cisplatin or M-VAC [19]. Nonetheless, immunotherapy is being actively tested in this setting through the completion of multiple trials in this setting. Special mention deserves the DANUBE trial (NCT 02516241) that tested the anti-PD-L1 durvalumab versus durvalumab plus the CTLA-4 inhibitor tremelimumab versus chemotherapy in the first line setting. This study completed accrual in 2016 and first results are expected for Q1 2018. Also, the trial IMvigor130 [NCT 02807636] and KEYNOTE-361 [NCT 02853305] are currently recruiting patients and testing chemotherapy versus immunotherapy versus the combination of both strategies in the same context utilizing atezolizumab and pembrolizumab, respectively.

Results of these trials are highly awaited as they could change a treatment paradigm that has not evolved much for the last three decades.

The Second Line and Beyond

Treatment beyond progression to platinum-based chemotherapy has been ill defined in patients with mUC. Multiple small phase II trials with either single agent or combinations utilizing taxanes, pemetrexed or targeted agents, among other compounds, have demonstrated response rates ranging from 0 to 68%, but generally short lasting and with no demonstrated impact in OS [20].

Only a phase III trial that compared vinflunine versus best supportive care in this setting demonstrated a modest but not statistically significant improvement in survival for the experimental arm leading to the approval of this drug in Europe (not in the US) and its variable use in clinical practice [21].

In this context, recently completed trials with immunotherapies have shown promising efficacy. Firstly, a Japanese phase 1/2 study with a cancer peptide vaccine (S-288310) treated 38 patients with chemo-resistant mUC with excellent tolerance and a promising 2-year OS rate of 32% [22]. Additional data in larger patient populations is needed but it appears to be a promising strategy.

More importantly, up to five different checkpoint inhibitors (atezolizumab, nivolumab, pembrolizumab, durvalumab and avelumab) have been recently tested with success in patients with mUC and progression after platinum-based combos leading to their approval by the regulatory authorities and their progressive incorporation into clinical practice [23–27].

Overall, these compounds are able to induce about a 20–25% response rate and one-year survival rates ranging from 37 to 57%. Although these trials do not have a very extended follow up, there seems to be a tendency towards a “long tail” of survival in a certain percentage of patients. Only a low fraction of patients present severe treatment-related adverse events.

Two trials deserve particular attention in this patient population, as they are the only phase III randomized studies. KEY-NOTE 045 is a phase III open-label randomized trial where 542 patients with mUC that recurred or progressed after platinum-based chemotherapy were assigned to either

three-weekly pembrolizumab at 200 mg or investigator's choice of chemotherapy (paclitaxel, docetaxel or vinflunine). Pembrolizumab was able to improve the OS (10.3 vs. 7.4 months) with a reduction in the risk of death of 27% (Hazard Ratio 0.73; 95 CI 0.59–0.91 $p = 0.002$). The arm of immunotherapy also had a lower rate of treatment related adverse events. This was true for any treatment related adverse event (60.9% vs. 90.2%) and specifically for those of grade 3–5 (15% vs. 49.4%) [27].

IMvigor 211 is another phase III study testing an anti-PD-L1 such as atezolizumab in patients with mUC and progression/recurrence after platinum-based chemotherapy. This trial included a larger population of 931 patients who received atezolizumab every 3 weeks at 1200 mg or chemotherapy as per investigator choice (paclitaxel, docetaxel or vinflunine). The primary endpoint was OS and it was tested hierarchically in patients with PD-L1 expression on $\geq 5\%$ (IC2/3) and $\geq 1\%$ (IC1/2/3) of immune cells and in the intention-to-treat (ITT) population. Despite a numerical improvement (11.1 vs. 10.6 months), atezolizumab was not associated with statistically significant longer OS in platinum- refractory mUC patients overexpressing PD-L1 (IC2/3) compared with the chemotherapy arm (HR = 0.87 [95% CI: 0.63–1.21]). The PD-L1 biomarker enriched for responses in both arms. Atezolizumab achieved well-tolerated, durable remissions in both PD-L1 positive and ITT groups. Safety data was consistent with previous studies with this compound [24].

In summary five drugs targeting the check-point pathways (pembrolizumab, atezolizumab, nivolumab, durvalumab and avelumab) have been approved for the treatment of platinum-treated mUC although data from phase III studies is only available for pembrolizumab and atezolizumab. These compounds have shown positive facts when compared with chemotherapy in terms of efficacy and safety and will most likely change the way these patients are treated in the near future. Yet, predictive biomarkers are lacking to help in adequate patient selection.

New Combinations

As reviewed in the previous sections, the single agent studies with immunotherapies (mostly checkpoint inhibitors) provided promising results both in first and subsequent lines of mUC. However, despite the novelty and expectation brought by these compounds only around 1 on 4 patients

with mUC will achieve a substantial benefit from checkpoint inhibition. These facts and a better knowledge of the interaction of the immune system with cancer cells has led to an intense drug development in the field posing special interest in combinations of different strategies.

Pharmaceutical development in this context has occurred according to the three immunological scenarios described in the literature (immune desert, immune excluded and inflamed). The so called ***immune desert***, are tumors where CD8⁺ T cells are absent from tumor and its periphery and therefore the need is to increase the number of antigen-specific T cells in the tumor or increase antigen presentation. In this scenario drug development has moved toward compounds that include a linker to adhere to the tumor cell and that have attached some form of immunotherapy. The monoclonal antibodies targeting CEA and fused to engineered cytokines such as IL2v are an example of such strategy. These compounds are being developed in combinations with checkpoint inhibitors such as atezolizumab (NCT 0230673). Other strategies in this context include the so-called antibody drug conjugates (ADC). These are immunoglobulins designed to bind specific tumor-associated antigens and that are conjugated to a cytotoxic that will be internalized upon immunoglobulin binding to the cancer cell. An example of this class of compounds is Enfortumab Vedotin, an ADC that comprises the human anti-nectin-4 antibody conjugated to a potent microtubules-disrupting agent called MMAE. Data on mUC patients treated with this drug was presented at ASCO 2017 with high response rates in a very heavily pre-treated population including 40% previously treated with checkpoint inhibitors [28]. Several studies are ongoing with this class of compounds.

The ***immune excluded*** tumors are those where there are immune cells in the periphery of the tumor but unable to infiltrate it. The key objective would be to bring T cells in contact with cancer cells. In this context the T cell bi-specific (TCB) antibodies have been developed. These compounds bind T lymphocytes and tumor cells simultaneously resulting in T cell activation and tumor cell destruction. These drugs such as the CEA-CD3 TCB are being currently tested both as single agents and in combination with anti-PD-L1 (i.e., [NCT02324257]). Lastly, those tumors considered ***inflamed*** include those neoplasms where CD8⁺ T cells have efficiently infiltrated the tumor but are not fully functional. The key objective in this setting is to stimulate the T-cell response by removing the physiological

brakes or by stimulating T-cell response. Inhibitors of the cytosolic enzyme indoleamine-pyrrole 2,3-dioxygenase (IDO), an endogenous regulator of local immune response through the metabolism of tryptophan, are being tested in combination with checkpoint inhibitors [NCT02471846]. Another strategy in this setting is unblocking an inhibitor of the immune response such as TIGIT. TIGIT downregulates T cells and natural killer cells. Combinations of antibodies anti-TIGIT with checkpoint inhibitors are ongoing and results highly awaited [NCT 02913313]. Lastly, acting on tumor associated macrophages (TAM) represents a complementary strategy in immunotherapy by depleting tumor-promoting TAM. Drugs targeting the colony stimulating factor 1 (CSF1) or its receptor (CSF1R) such as emactuzumab have shown activity by this mean and many other similar compounds are being actively tested.

Lastly, the following combination/sequencing strategies are currently being tested in the clinic. (1) Immunotherapy combos: The study Checkmate 901 evaluates nivolumab+ ipilimumab versus chemotherapy in first line mUC patients. The Danube study tests durvalumab plus tremelimumab versus durvalumab versus chemotherapy. (2) Immunotherapy + chemotherapy combos: This strategy is being tested similarly in two trials one with atezolizumab (IMvigor130) and one with pembrolizumab (KEYNOTE 361) with three arms (chemo versus chemo-immuno versus immuno). (3) Radiation combos. Several studies are combining checkpoint inhibitors with radiation both sequentially and concurrently. There is recent interest in the use of stereotactic body radiotherapy with immunotherapy [29]. (4) Sequential chemotherapy-immunotherapy. There are studies testing the value of administering an immunotherapy after achieving a favourable response with chemotherapy in mUC as a maintenance strategy (i.e., JAVELIN trial).

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Part IV

A View on the Future

13. The Role of Urologist

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Is Bladder Urothelial Carcinoma a Preventable Disease?

Bladder cancer (BC) is the 5th most common cancer with 429,793 new cases diagnosed each year worldwide and 79,030 only in USA [1]. It is most common in males with a 3:1 ratio [2]. Each year, it is estimated that more than 165 thousands patients with BC will die, representing the 10th most common cause of death due to cancer worldwide [2]. BC is one of the most expensive malignancies. The annual cost of BC in the USA in 2010 was four billion US\$ and is expected to rise to five billion US\$ by 2020 [3]. Current efforts to prevent BC are to avoid exposure to carcinogens such as occupational and/or smoking carcinogens.

Tobacco smoking is considered the most important risk factor for BC with more than 50% of patients diagnosed with BC having been exposed to smoking [4, 5]. The mechanism underlying this association is the carcinogenic effect of aromatic amines and polycyclic aromatic hydrocarbons in the urine of smokers. Tobacco use is the most preventable cause of cancer and death from cancer worldwide today. Therefore, urologists and other health providers should play an essential role by making a concrete effort to

guide smoking cessation efforts, in the teachable moment of BC diagnosis and indirectly through awareness and policy making [6].

Exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons due to occupational reasons is the second most important risk factor for BC. An estimated 10% of BC patients have a history of continuous exposure to these carcinogens. Exposure to these chemicals occurs mainly in industrial plants which process paint, dye, metal and petroleum products [7, 8]. A reduced risk was noticed in workers that are working under safety guidelines provided in countries with strict safety regulations of the industry [4, 7].

Other reported risk factors have a more moderate impact on BC development. Some of these factors include family history [9], genetic predisposition which may influence other risks factors associated with BC [10, 11], consumption of chlorinated [4] or arsenic exposed water [12], use of permanent hair dyes, dietary habits [13], and exposure to ionizing radiation [14].

From all risk factors for BC, cigarette smoking is the most preventable cause being responsible for 20% of deaths each year [15]. The World Health Organization estimates that smoking kills almost six million people worldwide yearly. Most deaths are in direct connection with tobacco use while more than 600,000 are due to second-hand smoke [16]. Smoking is also a leading cause of urological health problems and premature death. Secondary to them, cessation is the only practicable way to decrease tobacco-attributable deaths before 2050, because a reduction in uptake by adolescents until 2025 will induce effects only 25 years after [17].

Urologists have a key role in modifying the behavior of tobacco consumption. When encountering a patient who smokes, they should use this moment as a teachable instant with high efficiency [18]. Recent studies showed that patients who receive smoking cessation advice from their urologist have a greater chance of quitting tobacco [19]. Indeed, one of two smokers with newly diagnosed BC will quit smoking and be receptive to smoking cessation advice [6].

One method in which urologist can intervene is an active anti-smoking action in the form of a 5-min brief smoking cessation intervention, which could be easily incorporated into daily clinical practice [19]. An optimal smoking cessation strategy should be individualized and done in collaboration with specialized institutions [6]. In order to achieve permanent smoking cessation it remains important to assist patients closely and talk about: smoking cessation clinics, the telephone quit line, psychologist support, and patients supporting groups [20]. Furthermore, urologists can provide pharmacological alternatives to smoking such as Varenicline and bupropion [21]. Individually-delivered smoking cessation counselling can effectively assist smokers quit [22].

Awareness of smoking related urological diseases remains low in general population. Therefore, it is important for urologists to get involved in primary prevention, social campaigns and multidisciplinary health-promoting actions. Such intervention will undoubtedly improve overall health, but it may also lower the risk of kidney, prostate, and bladder cancers as well as erectile function and fertility [23–27].

Although, data is accruing to support the importance of smoking cessation in urological health and urologists increasingly providing advice on quitting, many

challenges to the universal adoption of smoking cessation counselling remain. There are no European or American urological guidelines or consensus statements directing urologists on appropriate strategies for providing smoking cessation counselling. Second, urologists frequently do not feel qualified to provide smoking cessation counselling, while only a fraction of urologists have had formal smoking cessation training themselves [28]. This in turn, may lead to a limited use of pharmacological smoking cessation therapy which has been shown to be beneficial in increasing quit rates. Third, pharmacological smoking cessation therapy is not fully reimbursed by health insurance in most European countries despite its proven efficacy and cost-effectiveness, which may ultimately deter its use and subsequently the number of successful quitters [29].

In order to address these hurdles in providing smoking cessation, knowledge of tobacco cessation and control actions should be considered for inclusion in the core curriculum of urological training. Moreover, establishment of practice pattern guidelines for smoking cessation counselling by the European Urology Association (EAU) and the American Urological Association (AUA) may provide a framework based on which urologists can offer quit advice. As advocates for our patients, we must accept the responsibility and better counsel our patients about the detrimental effects of smoking and assist them in cessation efforts to improve their general health and quality of life.

Take Home Messages

1. *Cigarette smoking is the most preventable cause of BC*
2. *Pharmacologic therapy combined with behavioral counseling are effective approaches that can help with smoking cessation*
3. *Occupational hazard criteria need to be established and followed strictly by various industries*

Early Detection of Bladder Cancer: How Can This Be Done Best Today?

Early detection of BC patients represents a key issue in the management disease. There is growing evidence that early detection of BC leads to earlier treatment thereby reducing cancer-specific mortality [30–33]. Nevertheless, mass screening is not cost-effective as the prevalence of BC in general population is 0.001%, and an increase prevalence is noticed only in people over 50 years old (0.67–1.13%) [34]. Data obtained from recent screening trials and theoretical considerations on cost-effectiveness issues of BC screening have revitalized this subject [35–37]. Screening of a highly selected high-risk population with increased disease prevalence may offer a solution to the problem [38].

To date, there are only few studies that have addressed screening for BC in a targeted high-risk population. Most screening cohorts reported low BC detection rates (0.03–1.64%) with only one study reporting 51.2%, by including a very high risk population

[39]. A summary of screening cohort studies [36–47] in the last decade are shown in Table 13.1.

Table 13.1 Summary of bladder cancer cohort screening studies in the last decade (2006–2016)

Study	Country	Cohort no.	Target population	Test used	Positive tests no./%	Diagnostic	BC (No./%)	Follow-up
Messing et al. [40]	USA	1575	Males >50 yr	Dipstick 14 d. and repeated 9 mo. later	258/16.4%	Cystoscopy	21/1.33%	Yes 14 yrs
Hedelin et al. [41]	Sweden	1096	60–70 yr males	Dipstick and UBC	174/15.9%	Cystoscopy	7/0.64%	No
Steiner et al. [36]	Austria	183	Smokers ≥40 pack-yrs	Dipstick, NMP22, cytology and UroVysion	75/41%	Cystoscopy	3/1.64%	No
Lotan et al. [38]	USA	1502	Both sex >50 yr Smokers (>10 yr) +/- professional exposure (> 15 yr)	NMP22	85/5.7%	Cystoscopy	2/0.13%	No
Roobol et al. ^a [42, 43]	The Netherlands	1747	50–75 yr males	Dipstick 14 d. If positive: NMP22, FGFR3, microsatellite, methylation	75/4.29%	Cystoscopy	4/0.22%	Yes [43] 2 yrs
Gilberti et al. [44]	Italy	152	Exp. PAHs	Dipstick, cytology and uCyt+	18/11.8%	Cystoscopy	–/–	No
Pesch et al. [45]	Germany	1323	Exp. AAs	Dipstick, blood cell count, cytology, NMP22 and UroVysion	–/–	Cistoscopy	14/1.06%	No
Zlotta et al. [39]	Belgium	48/38 completed follow-up	Aristolochic acid and 17 with history of UTUC	Cystoscopy every 6 mo. + systematic Bx	22/51.2%	Cystoscopy + Bx	22/51.2%	Yes 10 yrs
Huber et al. [46]	Germany	1609	AAs	NMP22	224/13.9%	Cystoscopy	6/0.03%	No
Taiwo et al. [47]	USA	7826	Coal tar pitch exposed area	Cytology and ImmunoCyt/uCyt	198/2%	Cystoscopy	14/0.17%	Yes 1 yr

Study	Country	Cohort no.	Target population	Test used	Positive tests no./%	Diagnostic	BC (No./%)	Follow-up
Starke et al. [37]	USA	925	Age $\geq$ 50 years, $\geq$ 10 pack-years (combination of packs of tobacco per day and years of smoking) smoking and/or $\geq$ 15 years environmental exposure	NMP22	57/6.16%	Cystoscopy	2/0.21% and 9/0.97% after follow-up	Yes 6.5 yrs

AAs aromatic amines, PAHs polycyclic aromatic hydrocarbons, UTUC upper tract urothelial carcinoma, NMP22 nuclear matrix protein 22, FGFR3 fibroblast growth factor receptor 3, d days, mo months, yr year

^aInitially only 1 BC found

Nowadays, the accepted standard for BC detection is Cystoscopy, which has some disadvantages as it is an invasive procedure, relatively expensive, with an approximately 10–20% false negative rate (missed tumors) when white light is used. New endoscopic technologies such as fluorescence or narrow-band imaging, increase detection rates but add extra costs. There is an unmet need for better, simpler, and cheaper diagnostic tests for BC detection [34, 48].

Voided urine cytology is a highly specific, noninvasive adjunct to cystoscopy. It has good sensitivity for detecting high-grade urothelial cancer, but its sensitivity for detection of low-grade tumors ranges only from 4 to 31% [49]. The accuracy of cytology depends upon the expertise and dedication of the pathologist [50]. Many laboratory and clinical investigations have developed numerous new urine markers to facilitate BC diagnosis. Most of them have superior sensitivity to urine cytology, especially in low grade cancers, but none outperforms the accuracy of cytology overall. Therefore, none of these tests is considered as a standard diagnostic procedure in clinical guidelines today [51, 52].

For a marker to be potentially clinically useful, it is necessary for it to show that adding it to an existing model based on the most important clinical and pathological factors substantively improves the predictive accuracy (discrimination and calibration) of the model [53]. An ideal marker must meet some requirements as its needs to be “easier, better, faster, and cheaper” [54]. There are some recent promising integrative models that included markers for BC early detection [55].

Take Home Messages

1. *BC screening in high-risk groups may allow identification of tumors before muscle invasion*
2. *Although BC screening is theoretically feasible in a high-risk population, there is currently insufficient evidence to recommend it based on cost-effectiveness*

3.

In future, improved definition of high risk populations suited for screening together with the development of integrated multi-markers models may improve detection of urothelial cancer in the entire urinary tract.

Intravesical Therapy for Bladder Cancer: What Is on the Horizon?

Intravesical Instillations with Bacillus Calmette-Guérin

Intravesical therapy is used either as adjuvant therapy after a complete endoscopic resection, or rarely, as adjuvant therapy with the goal of eradicating residual disease after (transurethral resection of bladder tumor) TURBT. This distinction is important, because most published data reflect the former, with the goal of preventing recurrence or delaying progression to a higher grade or stage.

When given prophylactically, bacillus Calmette-Guérin (BCG) has been shown to prevent BC recurrences after TURBT. Meta-analyses showed that BCG after TURBT is superior to TURBT alone or TURBT plus chemotherapy in preventing recurrences of high-grade Ta and T1 tumors [56–59]. A recent meta-analysis that included almost 3000 patients with non-muscle-invasive bladder cancer (NMIBC) reported that mitomycin C (MMC) was superior to BCG without maintenance in preventing both recurrence and progression, but inferior to BCG in trials with maintenance [60]. Using the SEER population-based database, patients receiving BCG therapy had a decreased mortality by 23%, but only 1 out of 5 patients who was eligible for BCG received indeed, the treatment. These findings suggest that BCG therapy is still underused in clinical practice [61].

BCG Strain in Therapy Success

The EAU guidelines on NMIBC (2017 update) [62] report no conclusive evidence among clinical efficacy of various BCG strains as a meta-analysis suggested no large differences in efficacy between various BCG strains [51]. However, new data suggests potential differences in efficacy of different BCG strains.

A prospective RCT by Rentsch et al. set out to establish if there was a difference in treatment outcomes between two commonly used strains of BCG, i.e., Connaught and Tice [63]. Patients with high-risk NMIBC were given six installations of either Connaught or Tice. The authors reported a statistically significant benefit of BCG Connaught over BCG Tice with respect to 5-year recurrence-free survival. There was no difference in BCG-related adverse effects. Analysis of the experimental data suggested a more pronounced Th1 response and greater T-cell recruitment in the bladders of BCG Connaught in in-vivo murine models.

Contrary, BCG Tice was superior to Connaught in a recent large retrospective multi-center study [64]. On the other hand, Guerrero-Ramos et al. reported no difference in

outcomes related to BCG strains [65] and another prospective study comparing BCG Tokyo 172 with BCG Connaught found no difference in complete response, recurrence-free survival or adverse event rates [66]. In the most recent meta-analysis that included 12,246 patients no bacillus Calmette-Guérin strain demonstrated significant superiority when compared to any other strain in preventing disease recurrence [67]. Recently, a study showed that if used in combination with IFN, there is no difference in recurrence-free survival regarding the strain of BCG [68].

Management of BCG Refractory Patients

Despite BCG therapy, almost 40% of patients will experience disease recurrence and 60–70% of these fail a repeat BCG induction. For such patients, radical cystectomy remains the preferred treatment option as stated by the AUA and EAU guidelines. Even so, some patients are medically unfit or will refuse radical surgery. Salvage intravesical therapies may preserve quality of life in these patients. There are numerous non-BCG intravesical salvage options available, including immunotherapy, single-agent chemotherapy, combination chemotherapy, and device-assisted chemotherapy. In addition, investigation of radiation-based treatment and other novel therapies including checkpoint inhibitors (programmed death-1/programmed death ligand-1), are currently underway [69].

Radiofrequency chemohyperthermia (CHT) and Electromotive Intravesical Drug Administration (EMDA) have been tested with encouraging results, as discussed in Chapter 3.3.

The definition, prediction, and treatment of BCG failure remain important areas of BC care and research. Patients with BCG failure need careful selection and individualized therapy in experienced hands. Stratification of patients with BCG failure into groups can identify those with a better or worse prognosis [70].

Valrubicin is the only salvage intravesical therapy approved for CIS or for patients who do not tolerate BCG [71, 72]. Alternatives under investigation include Mycobacterium cell wall-DNA complex [73, 74], gemcitabine [75–77], doublet intravesical chemotherapy with gemcitabine and mitomycin or docetaxel [78, 79], docetaxel [80, 81] or with paclitaxel (Abraxane®) [82, 83]. Main findings of these promising alternatives for BCG refractory patients are listed in Table 13.2. Current guidelines consider all option inferior to RC [62].

Table 13.2 Studies assessing the efficiency of alternative intravesical drugs for BCG failure patients

Study	Study type	Drug	Patients/control arm	Follow-up (months)	Main results
Steinberg et al. [71]	Single arm	Valrubicin 6 wks 800 mg	90	30	CR 21%
Dinney et al. [72]	Phase II/III RCT	Valrubicin 6 or 9 wk 800 mg	78	6	CR 18%

Study	Study type	Drug	Patients/control arm	Follow-up (months)	Main results
Morales et al. [73]	RCT	MCNA emulsion 6 wks 4 or 8 mg	25/30	18	CR 27.3% 4 mg CR 46.4% 8 mg
Morales et al. [74]	Single arm	MCNA 6 wks 8 mg	129	34.7	CR 25% at 1 yrs CR 19% at 2 yrs
Dalbagni et al. [75]	Single arm	Gemcitabine 2 wks 2000 mg/100 mL for 3 weeks	30	19	CR 21% at 1 yr
Skinner et al. [76]	Single arm/multi-center	Gemcitabine 2 g/100 mL 2×6 wks than monthly up to 12 mo.	47	24	CR 47% 3 mo., RFS 28% 1 yr RFS 21% 2 yr
Di Lorenzo et al. [77]	RCT	Gemcitabine 2 g/50 mL 2×6 wks than wk for 3 consecutive weeks At 3, 6 and 12 mo. BCG Connaught 81 mg/50 mL 6 wks than wk. for 3 consecutive weeks At 3, 6 and 12 mo.	40/40	24	CR 47.5% vs.12.5% 19% vs. 3% at 2 yr Progression 33% vs. 37.5%
Lightfoot et al. [78]	Single arm/multi-center	6 wks sequential gemcitabine 1 g and MMC 40 mg	47	26	CR 68%, RFS 48% 1 yr RFS 38% 2 yr
Steinberg et al. [79]	Single arm	6 wks sequential gemcitabine 1 g/50 mL and docetaxel 37.5 mg/50 mL	45	15	66%, RFS 54% 1 yr RFS 34% 2 yr
McKiernan et al. [80]	Single arm	6 wks Docetaxel starting dose 5 mg	18	2.5	CR 56%
Barlow et al. [81]	Single arm	6 wks Docetaxel starting dose 5 mg Maintenance monthly 12 mo.	54	39.1	CR 59%, RFS 40% 1 yr RFS 25% 3 yr, 24% RC
McKirnan et al. [82] Robins et al. [83]	Single arm	Nab-paclitaxel 500 mg/100 mL 6 wks	28	21 41	CR 35.7%, PFS 67.8% RFS 18%, OS 56%, CSS 91%

RCT randomized clinical trial, *wks* weeks, *mo* months, *yr* year, *CR* complete response, *MCNA* mycobacterial cell wall nucleic acid, *RFS* recurrence-free survival, *PFS* progression-free survival, *RC* radical cystectomy, *OS* overall survival, *CSS* cancer-specific survival

Take Home Messages

1. *BCG is still the best adjuvant treatment for intermediate and high-risk NMIBC*
2. *Radiofrequency CHT driven and EMDA MMC have promising results as alternative or salvage to BCG*
3. *For patients who experience BCG failure, to date, only Valrubicin is FDA approved therapy after BCG*

Revolution Through Precision Medicine and Immunotherapy?

After decades of skepticism, immunotherapy is poised to become a mainstay of cancer treatment [84]. Currently, the most promising approach in activating therapeutic antitumor immunity is the blockade of immune checkpoints [85] as well as the use of genetically engineered T cells with chimeric antigen receptor (CAR) directed against tumor associated antigens [86]. Treatment with BCG belongs to the most successful cancer immunotherapies, and in high-risk, non-muscle-invasive bladder cancer, it is the standard adjuvant treatment according to EAU guidelines [51]. Forty years after its introduction [87], the exact immune mechanism of BCG-induced antitumor activity is still not fully understood [88].

Several immune check point inhibitors [89–94] have shown promising results in clinical trials and started a new debate about the future role of this drugs in treatment of patients with advanced and metastatic BC (Table 13.3).

Table 13.3 Clinical trials with promising results using anti-PD-L1 and anti-PD-1 inhibitors for treatment of metastatic urothelial cancer

Registration no./phase	Publication	Drug used	Indication	Patients included/eligible	TRAE	Results
NCT0208652/II	Balar et al. [89]	Atezolizumab (1200 mg IV/3 weeks)	1st line, Cisplatin ineligible	123/119	Fatigue 30% Diarrhea 12% Pruritus 11% Deaths 0.8% Treatment discontinued 8%	ORR 17.2 mo. 23% (CI 16 to 31) DOR not achieved PFS 2.7 mo. (2.1 to 4.2) OS 15.9 mo. (10.4 to n.e)
	Rosenberg et al. [90]		Post-platinum	315/310	Any grade 69% Grade 3–4 16%	ORR 15% (CI 11 to 20) DOR not achieved

Registration no./phase	Publication	Drug used	Indication	Patients included/eligible	TRAE	Results
NCT01693562/I/II	Massarad et al. [91]	Durvalumab (10 mg/kg/2 weeks)	Unresectable or metastatic	61 40 PD-L1+ 21 PD-L1-	Any grade 63.9% Fatigue 13.1% Diarrhea 9.8% Grade 3 4.9% Treatment discontinued 1.6%	ORR 31% (CI 17.6 to 47.1) in all pts. ORR 46.4% in PD-L1+, 0% in PD-L1-
NCT01772004/I	Apolo et al. [92]	Avelumab (10 mg/kg/2 weeks)	Post-platinum or Cisplatin ineligible	44	Any grade 65.9% Fatigue 31.8% Infusion-related 20.5% Nausea 11.4% Grade 3–4 6.8% Treatment discontinued 1.6%	ORR 18.2% (CI 8.2 to 32.7) in all pts. ORR 53.8% in PD-L1+ and 4.2% in PD-L1- DOR not achieved OS 13.7 mo. (8.5 to n.e) PFS 11.6 w (6.1 to 17.4)
NCT02387996/II	Sharma et al. [93]	Nivolumab (3 mg/kg/ 2 weeks)	Unresectable or metastatic	270/265	Grade 3–4 18% 3 deaths 1.13%	ORR 19.6% (CI 15 to 24.9) in all pts. ORR 28.4% (18.9 to 39.5) in PD-L1 > 5%+ ORR 23.9% (16.5 to 32.3) in PD-L1 > 1%+ ORR 16.1% (10.5 to 23.1) in PD-L1 < 1%+ PFS 2 mo. (1.87 to 2.63) in all pts. OS 8.74 mo. (6.05 to n.e) in all pts.

Registration no./phase	Publication	Drug used	Indication	Patients included/eligible	TRAE	Results
NCT02256436/III	Bellmunt et al. [94]	Pembrolizumab (200 mg/3 weeks) vs. Chemotherapy (paclitaxel, docetaxel or vinflumine)	2nd line, Post-platinum	542	Any grade 60.9% vs. 90.2% Grade 3–5 15% vs. 49.4%	ORR 21.1 vs. 11.4% (p < 0.001) OS 10.3 mo. (8 to 11.8) in pembrolizumab pts. vs. 7.4 mo. (6.1 to 8.3) in chemo pts. (p = 0.002) OS 8 vs. 5.2 in PD-L1 ≥ 10% (p = 0.005) PFS 2.1 vs. 3 mo.

TRAE treatment-related adverse events, *ORR* objective response rate, *DOR* duration of response, *PFS* progression-free survival, *OS* overall survival, *n.e* not estimated

Current standard treatment for these patients is platinum based chemotherapy, which is characterized by a short and limited response rate accompanied by significant toxicity. The perspectives of immune checkpoint inhibitors use is both as first line therapy in patients considered unfit for cisplatin or as second-line therapy in patients who have experienced disease progression after platinum chemotherapy.

Most import is the identification of predictive factors in terms of efficacy and patients' stratification for immunotherapy as within all the clinical trials, 60–80% of patients do not respond to the PD-1/PD-L1 checkpoint blockades. From this point of view, it is crucial to identify a biomarker to predict the response to checkpoint inhibitors.

PD-L1 expression was studied as biomarker in many of the trials testing anti-PD-1 and anti-PD-L1 drugs, but PD-L1 staining has low predictive accuracy and presents dynamic changes which could not be used as a criteria to select patients for PD-1/PD-L1 pathway blockade [95]. Recently, it was shown that tumor infiltrating immune cells and molecules present in the tumor microenvironment could serve as predictive biomarkers together with PD-L1 expression [95].

In future, gene analysis (e.g., gene signatures, mutational landscape, and/or mismatch-repair deficiency) could help also in patients selection if preliminary studies will be confirmed and validated [89, 90]. The spread of immune checkpoint inhibitors in clinical practice will need both medical oncologists and urologists confidence with the identification and management of typical side effects associated which are still much less common and severe than in platinum based therapy [96].

As for the translation of trials results into clinical practice, unfortunately, we do not have a direct comparison between different anti-PD-1 and anti-PD-L1 compounds that are currently in clinical development. In the absence data regarding differences in efficacy of different PD-1/PD-L1 checkpoint blockaders, it will need time and more research efforts in order to establish the best treatment choice. Even more, we need to answer which is the

best dose-response relationship as recent evidence in melanoma with Ipilimumab suggests that higher dose is associated with higher efficacy [97], and which is the optimal duration of treatment that is continuous until disease progression or intermittent.

Ongoing trials should clarify also the role of immune checkpoint agents as first-line treatment, compared to platinum-based chemotherapy. Confirmation of promising results of these trials will lead to radical changes in treatment of patients with advanced BC compared to current guidelines.

Immunotherapy is an evolving field that offers promise even in the treatment of NMIBC. Although, BCG still remains the cornerstone treatment for high-grade NMIBC, the toxicity, limited efficacy in a subset of patients, and recurrence rates call for more effective treatment options. Recombinant BCG, monoclonal antibodies, vaccines, and adoptive immunotherapy are potential options aimed at addressing these shortcomings [98].

Take Home Messages

1. *PD-1/PD-L1 checkpoint blockades are approved therapies in second line metastatic BC and in first line cisplatin-ineligible BC because of their high efficacy and tolerability*
 2. *Knowledge of the side effects and experience in their management is essential to optimal patient care*
 3. *Biomarkers are awaited as the sequence and combination of checkpoint inhibitors with other drugs is rendering the field complex*
-

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14. A View of the Future: The Role of Pathologists

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Standardisation of Pathology Reports

Standardisation of pathology reports has become an essential step in the process of improving patient care. Not only to ensure that the same histological elements are reported, but also to allow more accurate comparison of different studies from different institutions or countries. During the last 20 years, the WHO classification made several steps toward standardisation by providing detailed description of different entities and histological elements to improve the quality of the reports [1, 2]. Another step forward was the ICCR (International Collaboration on Cancer Reporting) group, which was founded by major pathology organizations [3]. The main goal was to produce internationally standardized and evidence based datasets for the pathology reporting of cancer, in order to improve cancer patient outcomes worldwide and to advance international benchmarking in cancer management. The bladder dataset has been developed for the reporting of many specimen types including cystectomy,

cystoprostatectomy or diverticulectomy. The protocols apply to primary carcinomas (non-invasive and invasive), with or without associated epithelial lesions. Transurethral resection and biopsy specimens are dealt with in a separate dataset.

In the bladder datasets two types of elements were included: required (req) or recommended (rec). Required elements are those which are prognostically important and based on which clinical management is based. Evidence-based support at Level III-2 or above is needed for the element to be considered required. Required elements are mandatory reporting items that should be included in every pathology report. In comparison, recommended elements are those of which reporting may be clinically important and considered to be good practice but which are not yet validated or regularly used in patient management [3].

In the ICCR bladder datasets the following elements are included:

Clinical information (rec/req in TURB), specimen site (req), additional specimens submitted (req), operative procedure (req), bloc identification key (req/rec in TURB), histological tumour type (req), presence of non-invasive carcinoma (req), associated epithelial lesions (req/rec according to the operative procedure), histological grade (req), extent of invasion (req), macroscopic extent of invasion (req), microscopic extent of invasion (req), tumour focality (rec), substaging T1 disease (rec), lymphovascular invasion (req). Some items can only be applied in cystectomy specimen such as response to neoadjuvant therapy (rec), margin status (req), lymph node status (req), histologically confirmed distant metastases (req), coexistent pathology (rec) and pathologic staging (req if applicable) (see Table 14.1).

Table 14.1 Required and recommended items in a pathology report according to the ICCR

Item	Recommended	Required
Clinical information	+	+
Specimen site		+
Additional specimens submitted		+
Operative procedure		+
Bloc identification key	+(TURB)	+
Histological tumor type		+
Presence of invasive carcinoma		+
Associated epithelial lesions (depends on operative procedure)	+	+

Item	Recommended	Required
Histological grade		+
Extent of invasion		+
Macroscopic extent of invasion		+
Microscopic extent of invasion		+
Tumor focality	+	
Substaging T1 disease	+	
Lymphovascular invasion		+
Only for cystectomies		
Response to neoadjuvant therapy		+
Margin status		+
Lymph node status		+
Histologically confirmed metastasis		+
Coexistent pathology	+	
Histological staging (if applicable)	+	

The objective of providing uniform reporting and treatment for bladder cancer is expected to be facilitated by using these datasets along with the WHO 2016 and the EAU guidelines [1, 4].

Rare Tumors of the Bladder

The WHO 2016 classification redefined several entities of UC, especially the adenocarcinoma group was changed and the signet ring cell variant was added to the diffuse/plasmacytoid group. Other rare entities are the lymphoepithelioma, sarcomatoid, giant cell, undifferentiated, clear cell and lipid rich types.

In the pure non urothelial variant histologies, squamous cell carcinoma, glandular neoplasms, urachal carcinomas and tumours of Müllerian type such as clear cell carcinoma and endometrioid carcinoma, but also neuroendocrine carcinomas are very rare entities [1].

Three major issues are important in variant histologies . First the problem of recognition and implication on prognosis. Several studies could demonstrate different results according to an interobserver variability [5, 6], especially in non typical cases. Second, different histologies might require

different treatments, but still no major consensus exists, how to treat several of these variant histologies. Some stage matched studies tried to underline the importance of variant histologies, especially in advanced stages.

Williams and Kamat could demonstrate that urologists are aware of the importance of variant histologies, but the type of treatment which should be administered is completely unclear to many of them [7].

Third, these variant histologies should not be mistaken for metastasis from another primary. These lesions can also be difficult to be recognized as a metastasis of bladder origin, especially if squamous or glandular differentiation is present. Immunohistochemistry does not always help, still no 100% urothelial marker exists [8], and therefore the clinical history of the patient is helpful for the pathologist. Another useful step is comparing the slides of an initial tumor with the metastatic lesion, as well from a morphological point of view as immunophenotypic point of view.

It is important to underline that variant histology does not always mean bad prognosis. Some rare pure entities seem to have better outcomes than the classical urothelial carcinoma or mixed urothelial carcinomas with classical and variant histological aspects [9, 10].

Urologists should be aware that making a diagnosis of a variant histology is sample is pathologist depended, especially if the variant histology is not 100% typical. In case of small samples, a difference with histological findings on the cystectomy specimen is possible [8]. Most mixed forms seem to have outcomes which are closer to the classical aspects than to their variant histology, a 50% cut-off as prognosticator is probably wise.

Comments on T1 Subdivision

From pathological point of view it is important to note that the term “invasive urothelial carcinoma” indicates the presence of invasive tumour cells beneath the urothelial basement membrane including lamina propria (pT1). Urologists on the other hand may use this term in their daily practice to refer to muscle invasive disease (pT2).

As pT1 tumours are known to recur and progress more frequently than their pTa counterparts, urologists may tend to treat pT1 bladder cancer more aggressively, and early cystectomy may even be considered for pT1 tumors with high-risk features such as those associated with carcinoma in-situ or

aggressive urothelial carcinoma variants [11, 12]. Therefore accurate staging of pTa/T1 tumors and identifying potential progressors among patients with pT1 is of major clinical importance.

Several inter- and intraobserver reproducibility studies have been conducted [13]. Even in cases with good material without artefacts, interobserver discrepancy was shown to still exist among pathologists [13, 14]. In those same studies up to 10% of pTa tumors were reclassified as pT1 and up to 52% of pT1 were reclassified as pTa. Some authors have therefore suggested reviewing all primary pT1 bladder cancers by a genitourinary pathologist in order to improve diagnostic accuracy [15].

While it is difficult to list all causes of discrepancy related to pathological staging in bladder cancer, there are some histological issues that merit discussion, such as the recognition of early lamina propria invasion (pTa versus pT1) [15, 16]. A recent study with internationally known uropathologists annotated lamina propria invasion on virtual slides. The advantage of this study was that pathologists had to show precisely what they called “invasive”. This study revealed moderate agreement for bladder cancer invasiveness in the selected difficult transurethral bladder resections, with a majority consensus in 72% of the 25 cases and a multi-rater kappa score of 0.47 [13].

Substaging of pT1 tumours is an important issue. The WHO did not give any precise recommendations, including in the latest WHO bluebook which recommends substaging of pT1, but without mandating a specific way of recording the extent of invasion [1]. In 2016, the ICCR made a major effort by suggesting several detailed models of recording the extent of lamina propria invasion [3]. The two most commonly used and easiest to apply methods were determined to be recording muscularis mucosae (MM) invasion and the diameter/depth of the invasive focus. Most papers have tried to use the MM as a limit to subdivide pT1 tumours into 2 subgroups [16]. The largest study to date is the paper of Rouprêt et al. which included 587 pT1 cases with a single centralized pathologist’s analysis [17]. They divided pT1s into pT1a and b (above or into/beyond the MM). On multivariable analysis, pT1b tumours had a significantly worse recurrence-progression- and cancer specific survival. Based on this study and a literature review, three findings can be underlined: First, the ability to assess MM ranges from 58% to 100%. Furthermore, on univariate analysis MM invasion was a significant predictor of recurrence free survival, progression

free survival and cancer specific survival in 30%, 88%, and 81% of the studies, respectively. On multivariate analysis, the numbers were 25% for recurrence free survival, 82% for progression free survival and 50% for cancer specific survival. As the WHO recommended substaging pT1 tumours, the ICCR group considered that two methods of reporting should be suggested to the pathologists. Therefore extension in millimeter and/or staging according to the MM have been included as a “recommended” element to be enclosed in a TURB pathology report.

Handling and Reporting Lymph Node Dissections

Lymph node (LN) status and the pN stage are important elements for prognosis and therapy. LN dissection is the best method for assessing the LN status, but no standardized handling protocols exists to date [18]. Furthermore, sampling is left to the discretion of each pathologists [19]. Some authors have suggested that the number of lymph nodes detected is directly related to the number of containers within the specimen [20]. The number of positive lymph nodes and the total number of resected nodes was reported to be important and “lymph node density ” (LNs involved with tumor divided by the total number of LNs removed) has been reported as a prognostic factor in some studies. Stein et al. who have shown that patients with lymph node density of 20% or less had 43% 10-year recurrence-free survival compared with only 17% survival at 10 years when the LN density was greater than 20% (p 0.001). On multivariate analysis the total number of LN involved remained a significant and independent risk factor for recurrence-free and overall survival, which is reflected by the pN system [21]. According to those findings, and although optimal macroscopic handling of LN dissection specimens is crucial, urologists need to be aware of the technical challenges that such specimens represent. LN dissections are manually palpated and then dissected. A major problem is that very often these LNs are extensively infiltrated by fat, have elongated features and even when totally embedded, the count on the slide may not be evident. Even when rigid features are used to define a LN (capsule, subcapsular sinus and lymphoid tissue) it is still unclear what to consider lymphoid aggregates without capsule and how to account for them in case of invasion by UC [1]. Furthermore, when cutting a LN, a single curved node can give the impression of being two lymph nodes, but also small grossly not

annotated LNs may exist in the fat around a large node. Counting the number of LNs on the slides together with a gross description is probably more precise than relying only on the macroscopic description.

Another issue is the lack of consensus on how to handle the remaining fatty tissue around the manually palpable LNs. Total submission of LN dissections has been encouraged by several authors as it was shown to increase the number of detected LNs [22, 23]. This being said, cost and time should also be factored in as clear impact on survival has not been established yet by using those total embedding protocols.

Moreover, nodal cancer volume, the size of the largest metastatic tumour deposit and extranodal extension were also shown to be prognostically important [24]. The issue of micrometastases is on the other hand not completely resolved, and although no recommendations for optimal section cutting are yet available, routine step sectioning and immunohistochemical staining are not recommended. A recent related paper from Engvad et al. argued against the routine use of cytokeratin staining, but advocated extensive pathological examination of LN dissections as a superior method for the detection of occult metastases [25].

Also worth mentioning is the issue of LN dissections post-neoadjuvant chemotherapy. In that regard there is no robust data indicating whether the number of LNs decreases after neoadjuvant chemotherapy. Similarly, there are no recommendations on the best way of reporting involution of lymph node metastases post-chemotherapy [25].

The ICCR has recommended the reporting of the following histological elements: number of LNs examined, number of positive LNs, presence/absence of extracapsular spread (recommended), size of the largest metastases (in mm). It is our opinion that reporting the size of the positive LN may also be of importance as it gives an idea of the extent of individual lymph node's involvement [3].

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15. The Role of Medical Oncologist

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Introduction

Unlike some other cancers, most patients with bladder cancer experience only a local disease, a phenomenon which has resulted in a relative down-playing of the role of systemic therapy and, thus, the domain of the medical oncologist in their care. Despite this, nearly all deaths which are directly attributed to bladder cancer result from disseminated disease. Furthermore, existing clinical diagnostic and staging tools are effective at identifying the patients who are at the highest risk of metastatic disease, and so the role of the oncologist in the care of patients with bladder cancer is becoming much better defined.

Current Position

The current position of the medical oncologist is clear in those patients who have metastatic disease at the time of diagnosis, or who develop metastatic disease following radical treatment. Here, the medical oncologist, often in parallel with the radiation oncologist and the palliative care team, manage a

disease which, for most, is incurable and, all too often, rapidly fatal. Cytotoxic chemotherapy plays a role in around 60% of these patients [1], and, more recently, a role has emerged for immunotherapy. Despite the clear efficacy of both classes of treatment, the overall benefits are modest and it is essential that the individual patient is able to make an informed choice about which treatment is most suited to their needs and expectations. The objectives of treatment at this stage of the disease are to optimize symptom-control, to maximize and maintain quality of life and to prolong overall survival. Thus, management of treatment toxicity is integral to achieving these objectives. As all of the drugs used to treat advanced bladder cancer are also widely used in other solid tumours, a common approach to toxicity management, often delivered by a multidisciplinary support team within a specialist oncology centre, may be associated with better outcomes. This is particularly pertinent to immunotherapy where potentially life-threatening immune toxicities, if recognized early, can be contained to permit ongoing high-quality survival.

But systemic therapy has also been proven, beyond reasonable doubt, to deliver survival gains if given as part of multi-modality treatment to patients with muscle-invasive, organ-confined disease. Level one evidence suggests an absolute survival gain of around 5–7% for neo-adjuvant chemotherapy given prior to cystectomy or radical radiotherapy [2, 3]. Furthermore, where neoadjuvant chemotherapy is not delivered, there is now strong evidence from meta-analysis to support the use of adjuvant chemotherapy for those with muscle invasive cancer at the time of cystectomy and this is also reflected in guidelines. Despite this, uptake of both treatments is low, even in high income healthcare environments [4]. Thus, it seems likely that there are barriers to accessing medical oncology input in the care of these patients and that, in many cases, the medical oncologist is still not fully engaged in the multidisciplinary care of patients with muscle-invasive bladder cancer.

In an era of extreme site specialization by oncologists, relatively few have specialized in the treatment of bladder cancer—most focusing more broadly on urological cancers with prostate cancer being the dominant disease. As a result, the role of the oncologist in the bladder cancer multidisciplinary team is poorly developed in many centres.

Current Barriers to Effective Medical Oncology Treatment

The precise nature of the barriers to accessing medical oncology treatments are poorly understood. Undoubtedly, the modest size of the benefit in muscle invasive disease combined with the relatively high level of expected toxicity from cisplatin-based chemotherapy forms a barrier both to referral and also to uptake. However, similar gains attributed to similarly toxic treatments are seen in other cancers where uptake of treatment is much higher (for example the addition of anthracycline chemotherapy to adjuvant chemotherapy regimens in early breast cancer [5]). The relatively high level of comorbidity seen in the bladder cancer population may underlie poor uptake of chemotherapy in the peri-operative setting particularly given the absence of evidence to support the use of non-cisplatin containing regimens.

It is also possible that there are organizational access barriers. In most countries organ-confined bladder cancer, regardless of stage, is managed exclusively within urology services without engagement from oncologists. It is possible, therefore, that opportunities for intervention are missed or that appropriate referral pathways simply don't exist. In addition, the reality of delivering neoadjuvant chemotherapy in standard care can result in delays in surgery which are considered unacceptable to both surgeons and patients [6]. Furthermore, recovery times from cystectomy are often such that the initiation of adjuvant chemotherapy in a realistic timeframe is challenging.

The lack of level 1 evidence to support the use of adjuvant chemotherapy has also led to genuine uncertainties about the value of this intervention in all groups of patients with muscle invasive bladder cancer (for example those with T2 or node positive disease).

A recent real-world study of patients with advanced bladder cancer in the USA revealed that 40% of patients never received systemic therapy. This reflects the fact that many patients present late in the course of the disease or with such significant comorbidity that such interventions are inappropriate. Furthermore, given the relatively modest benefits and potentially high toxicities of chemotherapy, even well-informed, otherwise suitable patients may choose best supportive care.

Future Perspectives

New Drugs Driving Multi-Modality Care

The advent of immune checkpoint inhibitors (those targeting PD(L)-1 and CTLA4) is already beginning to change the way advanced bladder cancer is treated. Despite the relatively modest response rates seen in first-line treatment and the absence of randomized data, high reported uptake of these drugs in the first line setting suggests that many patients and clinicians are willing to accept these treatments either as an alternative to chemotherapy or in situations where chemotherapy would not previously have been given at all. The efficacy of these drugs appears to be driven by a small proportion of patients who experience very durable responses. In diseases, such as melanoma, where checkpoint inhibitor trials have been followed up for several years, it appears that there is a significant number of patients who are long-term beneficiaries, and early follow up findings in urothelial bladder cancer are compatible with a similar effect. Furthermore, the tolerability profile of PD(L)-1 targeted therapy is such that many patients are prepared to try it in the hope that they may be such a beneficiary. Several randomized phase III trials in the peri-operative setting are underway. If these trials are positive, then it is likely that the new interventions will not only improve outcomes where used in combination (either simultaneously or sequentially) with chemotherapy but also broaden access to systemic peri-operative therapy to a wider group of patients. It is, therefore, likely that the oncologist will become a more relevant member of the multi-disciplinary team for a wider group of patients with muscle invasive bladder cancer. Although the checkpoint inhibitors' safety and tolerability profiles are generally good, the unpredictable nature of severe immune toxicity and the widespread use of these drugs across multiple tumour types means that acute care needs of patients receiving these treatments will likely be met by larger, broader specialist teams (embedded within oncology services in many centres).

Molecular Pathology Becomes Standard Practice

The advent of the immune checkpoint inhibitors has left us with a stark reminder of the urgency of the need to develop and implement predictive biomarkers into routine care. Current data suggest that a sizeable majority of patients do not benefit from these new drugs but are, nonetheless,

prepared to forego chemotherapy as a first treatment for advanced disease. Attempts to predict who will benefit (and, conversely, those whose needs may be better met with chemotherapy or supportive care alone) using PDL-1 immunohistochemistry have, by and large, failed so far in urothelial cancer [7]. Despite this, bladder cancer is a highly molecularly heterogeneous disease and our understanding of this heterogeneity is beginning to impact on our practice in other ways. Several groups have applied gene-array-based classifiers to urothelial cancer with several commonalities in their findings. Such molecular classifiers promise to identify subtypes of disease with different prognoses, but also with differing responses to treatment. In an analogous setting, similar classifiers applied to breast cancer now dictate systemic treatment priorities for subgroups of patients. Furthermore, there are specific molecular aberrations present in some patients with urothelial cancer which are potentially “actionable” with targeted therapies—an approach which has brought therapeutic success in other diseases such as lung cancer (for example the use of erlotinib in patients with activating mutations in EGFR, or crizotinib in patients with activation of ALK). Although early experiences selecting EGFR-targeted therapies for molecular subpopulations showed no impact, trials are underway exploring molecular pathology targets including FGF pathway aberrations and DNA-repair deficiency with FGFR inhibitors and PARP inhibitors respectively. Novel trial designs (e.g., ATLANTIS and BISCAY) (ISRCTN25859465; NCT02546661) now permit multiple biomarker/drug combinations to be explored simultaneously.

Thus, despite disappointing results to date, it is inevitable that future treatment choices will be guided, at least in part, by molecular pathology findings, and the medical oncologist will, in all likelihood, be the lynchpin in interpreting these data at a patient level.

Broadening the Scope of Multi-Modality Therapy

In addition to their established role in treating advanced disease and in the peri-operative setting, drugs also have a growing role in the context of radical radiotherapy, both as neoadjuvant treatment to reduce the risk of distant failure, but also as radiosensitizers to enhance local control. This multimodality approach will, for some, offer a bladder-preserving alternative to cystectomy.

Non-muscle invasive bladder cancer is generally regarded as a local disease and, thus, remains the preserve of the urological surgeon. However, there is a growing need for better tools to reduce the risk of local progression for patients at the high-risk end of the disease spectrum and in those in whom conventional approaches (namely intravesical BCG instillations) have failed. The growing evidence to support the role of immunotherapy in more advanced stages of the disease has led to an interest in harnessing the new and emerging immune treatments in high risk non-muscle invasive bladder cancer. Several trials are ongoing with immune checkpoint inhibitors (delivered both systemically and intravesically). Although this therapeutic hypothesis remains to be proven, it is likely that this group of patients, which previously were not considered by oncologists, may require oncological input into multimodality care.

Summary

The multi-disciplinary care approach is now the accepted norm for most common solid tumours in most healthcare environments. It appears that bladder cancer is only now arriving at this table, and that many patients still face barriers to accessing oncological interventions. With the first new effective drugs to emerge in over 20 years, we can now begin to address some of these barriers as treatment becomes suitable for a wider section of the patient population. As we move into the age of molecular stratification and precision medicine, a streamlined engagement between surgeons, medical oncologists and radiation oncologists has the potential to improve outcomes and better meet the needs of patient with bladder cancer.

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16. The Future of Radiotherapy in Bladder Cancer

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Questions

1. What are the current challenges in improving outcome of muscle-invasive bladder cancer (MIBC) patients treated with radical radiotherapy
2. Which predictive biomarkers hold the potential to guide selection of patients suitable for bladder preservation?
3. Are there clinically useful biomarkers to guide radiosensitizer selection?
4. What promise does the combination of immunotherapy and radiotherapy hold in MIBC?
5. How would the advances in technical radiotherapy improve tumour control while reducing toxicity of treatment?

Current Challenges

There is robust evidence to suggest that a bladder preserving strategy with trans-urethral resection of bladder tumour (TURBT) followed by radical radiotherapy with a radiosensitizer is in clinical equipoise with radical cystectomy in patients with localized MIBC [1, 2]. In the absence of any evidence of superiority of either approach the choice between radical radiotherapy or cystectomy is often a matter of patient and physician preference. Although multifocality, hydronephrosis and the presence of carcinoma-in-situ are considered relative contraindications for bladder preservation, there are no validated predictive biomarkers to objectively guide selection of patients suitable for either approach [1].

The use of a concurrent radiosensitizer results in outcomes superior to radiotherapy alone. The BC2001 trial demonstrated an improved loco-regional disease-free survival in favour of chemoradiotherapy with concurrent 5FU and mitomycin-c [3]. The benefit of the hypoxia modifying agents carbogen and nicotinamide (CON) with radical radiotherapy was established in the BCON trial [4]. Gemcitabine and cisplatin are also used as radiosensitizers in MIBC [5, 6]. There are no comparative data of the superiority of one radiosensitizer over another and their use is based upon patient and physician preference.

Conventionally, radical radiotherapy is delivered with an empty bladder and the target volume includes the entire bladder and any extra-vesicle tumour extension with a margin of around 1.5–2 cm for organ motion and set-up errors. Since the bladder is a mobile and deformable structure, its volume can vary markedly during a course of radiotherapy. One study reported that more of half of all treatment may be delivered with some element of “geometric miss” despite employing safety margins of 1.5 cm around an empty bladder [7]. Geometric miss reduces the probability of tumour control but expanding margins to ensure better tumour coverage would increase the volume of normal tissue exposed to high dose radiation leading to increased toxicity.

The incorporation of cone beam computed tomography imaging (CBCT) to radiotherapy delivery has enabled the direct visualisation of bladder position and target volumes in the treatment room, resulting in the

era of image-guided radiotherapy (IGRT) and adaptive radiotherapy [8]. A commonly used IGRT strategy involves generating a library of radiotherapy plans based on varying bladder volumes and selecting the most appropriate plan at the time of delivery based on CBCT imaging [9]. This “plan of the day” treatment approach improves the therapeutic ratio by reducing both the risk of geometric miss and volume of normal tissue irradiated [9]. However, since treatment plans are generated based on imaging at the time of simulation a margin for setup error and bladder motion still needs to be incorporated.

Attempts at escalating dose to the tumour bed while sparing dose to involved bladder tissues failed to result in any tangible reduction in toxicity and treatment outcome was largely similar [10, 11]. These studies were conducted prior to the advent of IGRT and newer studies looking at reducing treatment volumes and escalating dose to tumour are underway. Further controversies exist with regards to the need for including loco-regional nodes in the target volumes for radiotherapy. The rationale for irradiating pelvic lymph nodes is supported by data from surgical series’ which suggest that micro-metastases could be demonstrated in nearly one third of cases with clinically and radiologically negative nodes [12]. In patients undergoing radical surgery, dissection of the pelvic lymph nodes resulted in a superior survival [12]. However, studies investigating pelvic nodal radiotherapy have not revealed a consistent improvement in outcome and consequently there is a lack of consensus on the benefit of pelvic nodal irradiation in patients treated with a bladder preservation approach [3, 13].

Future Prospects

Radiotherapy exerts its cytotoxic effect predominantly by causing irreparable double-stranded DNA damage. Paradoxically, higher expression of DNA repair proteins leads to increased radiosensitivity probably by causing upregulation of cell cycle checkpoint inhibitors and activation of apoptotic pathways [14]. MRE11 is an enzyme which plays a major role in non-homologous end-joining repair of DNA double strand breaks [15]. Choudhury et al. found that high levels of MRE11 expression favourably predicts cancer specific survival in MIBC patients treated with radical radiotherapy, but not in patients treated with radical cystectomy [16]. These findings were independently reproduced by Lauberg et al. [17] If

prospectively validated in a clinical trial, MRE11 expression could fulfil the need of a predictive biomarker to select patients suitable for a bladder preservation approach.

Tumour hypoxia is a long-recognised cause of radioresistance [18]. The presence of molecular oxygen enhances the effect of radiotherapy by leading to the formation of peroxyl radicals which cause DNA double strand breaks in tumour cells [19]. The selection of hypoxia modification against systemic chemotherapy as a means of tumour sensitisation may be predicted by markers of tumour hypoxia. The heterogeneity of the tumour microenvironment and difficulties in measuring levels of hypoxia means that prediction of response to hypoxia modification is challenging. The development of potential biomarkers has focused on hypoxia-related protein expression, gene expression signatures and histological examination. Tumour necrosis (Fig. 16.1), a histopathological end-point in hypoxia, was shown to be a prognostic and predictive biomarker in the BCON trial [20]. The expression of hypoxia-associated proteins such as hypoxia-inducible factor (HIF)-1 α , CAIX and Glut-1 are also associated with a poor prognosis [21]. A retrospective analysis of patients enrolled in the BCON study revealed that high expression of HIF-1 α predicted benefit from hypoxia modification with CON [21]. There was no predictive benefit with CAIX and Glut-1 gene expression [21]. In addition, recently presented data suggest that a novel hypoxia gene expression signature could function as a valid predictive biomarker of benefit from hypoxia modification [22]. While the results of these retrospective analyses are encouraging, potential biomarkers would need further validation in prospective clinical trials prior to clinical application.

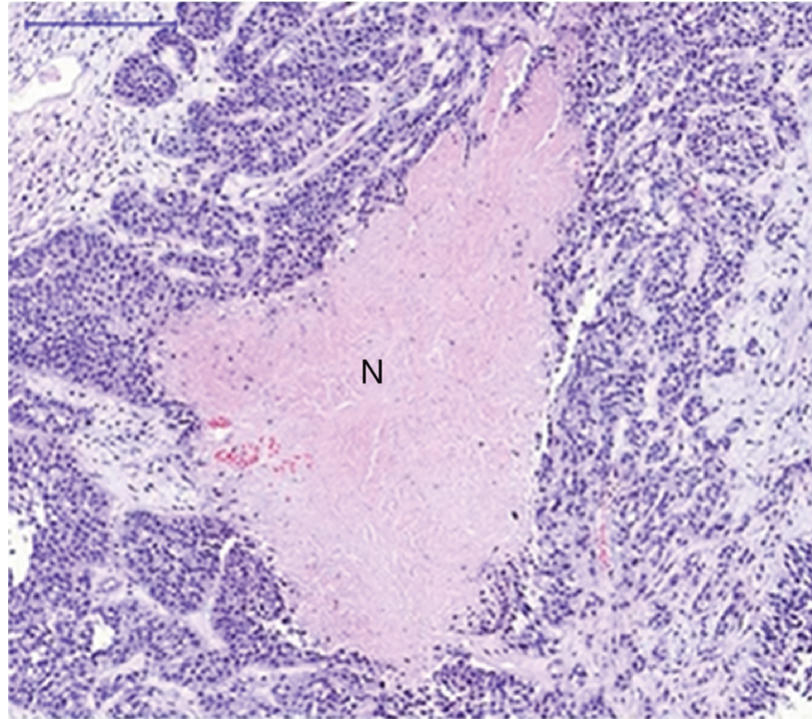


Fig. 16.1 Transurethral resection of urothelial cancer showing evidence of tumour necrosis (N)

The combination of immunotherapy and radiotherapy is emerging as a promising approach in many tumour sites including MIBC [23]. Radiotherapy induced cell death and its direct effect on the tumour microenvironment leads to activation of both the innate and adaptive arms of the immune system. The development of an anti-tumour immune response not only enhances local tumour cytotoxicity but may also lead to tumour regression at sites far removed from the radiotherapy field, a phenomenon known as the “abscopal effect” [23, 24].

Wu et al. demonstrated that irradiation up-regulates the expression of Programmed cell death ligand-1 (PD-L1) in bladder cancer cells and that increased expression of PD-L1 causes radioresistance by inhibition of CD8⁺ cytotoxic T cells [25]. It was further discovered that PD-L1 blockade augmented radiotherapy induced tumour cell death in pre-clinical models of bladder cancer [25]. The benefit of the anti-PD1 receptor antibody pembrolizumab in combination with radical radiotherapy is now being explored in ongoing clinical trials in MIBC [23].

Given the existing controversies in radiosensitiser selection in MIBC, predictive biomarkers are needed for selection of patients suitable for a combination approach incorporating radiotherapy and immunotherapy. In

studies of anti-PD1 therapy in advanced bladder cancer, expression of PD-L1 in tumour cells was associated with a better therapeutic response [26, 27]. However, most PD-L1 positive tumours did not respond to treatment and some PD-L1 negative tumours elicited a benefit [26, 27]. Therefore, the role of PD-L1 expression as a predictive biomarker of therapeutic benefit is uncertain and the search for more precise biomarkers continues. Pre-treatment lymphocytopenia has been identified as an adverse prognostic biomarker in MIBC patients treated with chemoradiotherapy and may reflect a state of cancer-induced immune incompetence [28]. If validated, peripheral blood lymphocytopenia could function as a simple biomarker to guide patient selection for immune modulation.

Adaptive radiotherapy and IGRT have the potential to enable escalating dose to the tumour while sparing uninvolved bladder tissue. In the BC2001 study, conventional imaging and use of bladder maps at the time of transurethral resection of bladder tumour (TURBT) was used with good effect to improve tumour delineation [10]. There is good evidence that diffusion weighted magnetic resonance (MR) imaging and use of fiducial markers such as gold seeds or lipiodol will permit tumour delineation with greater precision [29–31]. The randomized phase II RAIDER study in the United Kingdom, utilises these techniques to test the benefit of tumour focused boost and de-escalation of dose to uninvolved bladder tissues in MIBC [32]. If proven, this approach will change the current paradigm of whole bladder irradiation.

Although there is a lack of consensus on the merits of pelvic nodal radiotherapy in MIBC, there is no doubt that certain subgroups of patients at high risk of possessing occult lymph node metastases would benefit from such treatment. Unfortunately, MR and PET/CT imaging has failed to improve upon conventional size and anatomic criteria to detect occult lymph node spread and more accurate predictive imaging biomarkers to guide the selection of patients benefitting from pelvic nodal radiotherapy remains an unmet clinical need [33].

The advent of a MR-Linac system will make MR guided adaptive radiotherapy a reality, allowing personalized delivery of radiotherapy [34]. Online MR imaging during radiotherapy enables superior visualization of soft-tissues in comparison to CBCT based IGRT and has the potential to substantially reduce geometric uncertainties [35]. The superiority of MR imaging in defining bladder volume is shown in Fig. 16.2. However,

prospective studies are needed to confirm that the presumed therapeutic gains of MR guided adaptive radiotherapy is translated into clinical benefit in terms of tumour control and reduced toxicity.

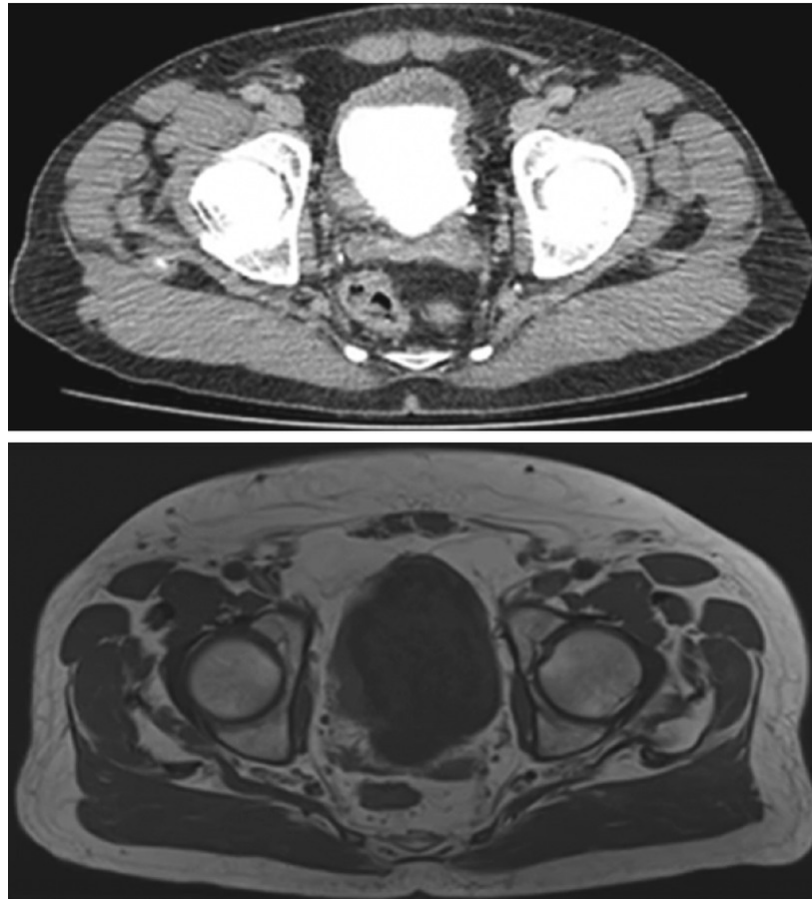


Fig. 16.2 The contrast between CT (above) and MR (below) imaging in visualising bladder volume

Figure 16.3 depicts a flow chart for personalized treatment in the setting of multi-modality bladder preservation.

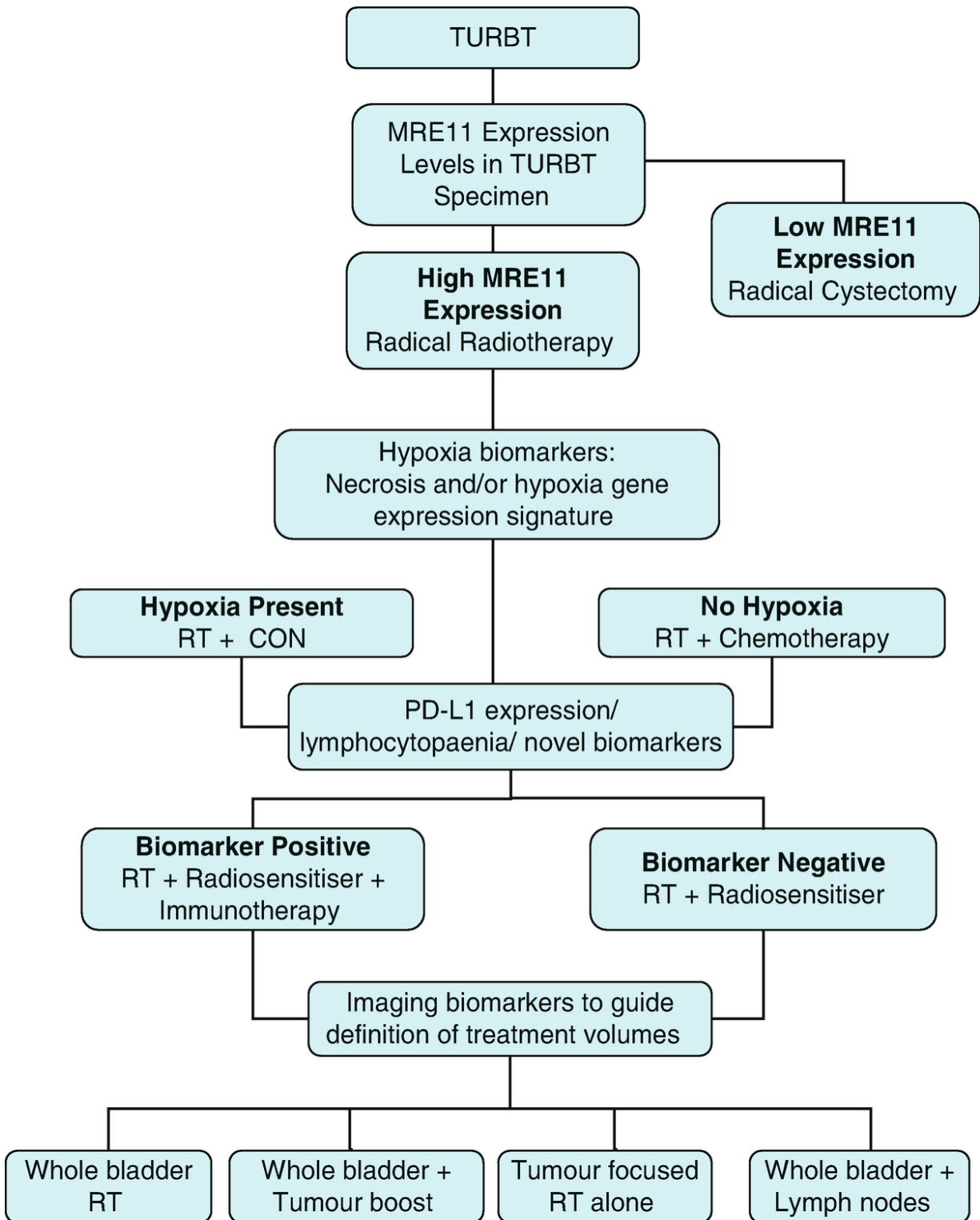


Fig. 16.3 Flowchart of personalized therapy with bladder preservation in the future. *RT* radiotherapy, *CON* carbogen and nicotinamide, *PD-L1* programmed cell death ligand-1

Take Home Message Although the therapeutic benefit of radical radiotherapy is well established, there is a lack of consensus on patient selection, choice of radiosensitiser as well as treatment volumes in the setting of a bladder preservation strategy, mainly due to the paucity of validated predictive biomarkers. While recent advances in technical radiotherapy have resulted in greater precision in the delivery of radiation therapy, variability of bladder volume and position continues to remain a significant challenge.

Further advances in technical radiotherapy and biomarker driven clinical trials in MIBC hold the potential to herald the dawn of an era of truly personalised therapy where objective criteria would determine patient selection for bladder preservation and the use of appropriate radiosensitisers, in addition to a tumour focused approach in the delivery of radiotherapy.

Answers to Questions

1. There is a paucity of objective criteria to guide patient selection in addition to controversies on the choice of radiosensitisers. Further controversies exist on the need for irradiation of pelvic lymph nodes and tumour focused dose escalation
2. Independent studies have confirmed the predictive value of MRE11 as marker of radiotherapy response in MIBC, but prospective clinical trials are needed prior to clinical application.
3. There are no validated biomarkers for prediction of benefit from use of individual radiosensitizers in MIBC. However, retrospective data have revealed that the presence of tumour necrosis, expression of HIF-1a and hypoxia gene expression signatures could help select patients suitable for hypoxia modification with CON. These biomarkers need prospective confirmation in clinical trials.
4. Pre-clinical data suggests a potential role for checkpoint inhibitors in combination with radiotherapy in MIBC. Clinical trials of pembrolizumab and radiotherapy are currently ongoing. However, PD-L1 expression remains a poor predictive biomarker of benefit from such an approach and more precise biomarkers are needed.

5. MR guided adaptive radiotherapy and the advent of the MR-Linac could potentially reduce geometric uncertainties in the delivery of radiotherapy to very low levels enabling improvement in the therapeutic ratio by escalating dose to tumour while sparing normal tissues.
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